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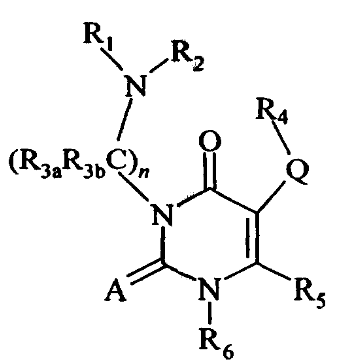
(54) Title: GONADOTROPIN-RELEASING HORMONE RECEPTOR ANTAGONISTS AND METHODS RELATING THERETO



(I)

(57) Abstract: GnRH receptor antagonists are disclosed which have utility in the treatment of a variety of sex-hormone related conditions in both men and women. The compounds of this invention have the structure of formula (I) wherein A, Q, R_1, R_2, R_{3a}, R_{3b}, R_4, R_5, R_6 and *n* are as defined herein, including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof. Also disclosed are compositions containing a compound of this invention in combination with a pharmaceutically acceptable carrier, as well as methods relating to the use thereof for antagonizing gonadotropin-releasing hormone in a subject in need thereof.

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GONADOTROPIN-RELEASING HORMONE RECEPTOR ANTAGONISTS AND METHODS RELATING THERETO

STATEMENT OF GOVERNMENT INTEREST

Partial funding of the work described herein was provided by the U.S. Government under Grant No. R43-HD38625 provided by the National Institutes of Health. The U.S. Government may have certain rights in this invention.

TECHNICAL FIELD

This invention relates generally to gonadotropin-releasing hormone (GnRH) receptor antagonists, and to methods of treating disorders by administration of such antagonists to a warm-blooded animal in need thereof.

BACKGROUND OF THE INVENTION

Gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone (LHRH), is a decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2) that plays an important role in human reproduction. GnRH is released from the hypothalamus and acts on the pituitary gland to stimulate the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH released from the pituitary gland is responsible for the regulation of gonadal steroid production in both males and females, while FSH regulates spermatogenesis in males and follicular development in females.

Due to its biological importance, synthetic antagonists and agonists to GnRH have been the focus of considerable attention, particularly in the context of prostate cancer, breast cancer, endometriosis, uterine leiomyoma, and precocious puberty. For example, peptidic GnRH agonists, such as leuprorelin (pGlu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt), have been used to treat such conditions. Such agonists appear to function by binding to the GnRH receptor in the pituitary gonadotropins, thereby inducing the synthesis and release of gonadotropins. Chronic administration of GnRH agonists depletes gonadotropins and subsequently down-regulates the receptor,

resulting in suppression of steroidal hormones after some period of time (*e.g.*, on the order of 2-3 weeks following initiation of chronic administration).

In contrast, GnRH antagonists are believed to suppress gonadotropins from the onset, and thus have received the most attention over the past two decades. To date, some of the primary obstacles to the clinical use of such antagonists have been their relatively low bioavailability and adverse side effects caused by histamine release. However, several peptidic antagonists with low histamine release properties have been reported, although they still must be delivered via sustained delivery routes (such as subcutaneous injection or intranasal spray) due to limited bioavailability.

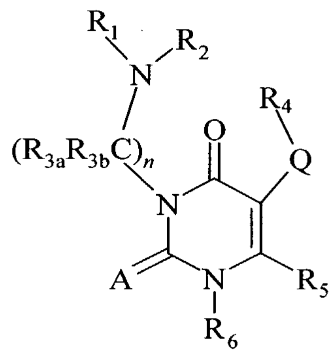
In view of the limitations associated with peptidic GnRH antagonists, a number of nonpeptidic compounds have been proposed. For example, Cho et al. (*J. Med. Chem. 41*:4190-4195, 1998) discloses thieno[2,3-*b*]pyridin-4-ones for use as GnRH receptor antagonists; U.S. Patent Nos. 5,780,437 and 5,849,764 teach substituted indoles as GnRH receptor antagonists (as do published PCTs WO 97/21704, 98/55479, 98/55470, 98/55116, 98/55119, 97/21707, 97/21703 and 97/21435); published PCT WO 96/38438 discloses tricyclic diazepines as GnRH receptor antagonists; published PCTs WO97/14682, 97/14697 and 99/09033 disclose quinoline and thienopyridine derivatives as GnRH antagonists; published PCTs WO 97/44037, 97/44041, 97/44321 and 97/44339 teach substituted quinolin-2-ones as GnRH receptor antagonists; and published PCT WO 99/33831 discloses certain phenyl-substituted fused nitrogen-containing bicyclic compounds as GnRH receptor antagonists.

While significant strides have been made in this field, there remains a need in the art for effective small molecule GnRH receptor antagonists. There is also a need for pharmaceutical compositions containing such GnRH receptor antagonists, as well as methods relating to the use thereof to treat, for example, sex-hormone related conditions. The present invention fulfills these needs, and provides other related advantages.

SUMMARY OF THE INVENTION

In brief, this invention is generally directed to gonadotropin-releasing

hormone (GnRH) receptor antagonists, as well as to methods for their preparation and use, and to pharmaceutical compositions containing the same. More specifically, the GnRH receptor antagonists of this invention are compounds having the following general structure (I):



(I)

including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof, wherein A, Q, R_1, R_2, R_{3a}, R_{3b}, R_4, R_5, R_6, and *n* are as defined below.

The GnRH receptor antagonists of this invention have utility over a wide range of therapeutic applications, and may be used to treat a variety of sex-hormone related conditions in both men and women, as well as a mammal in general (also referred to herein as a "subject"). For example, such conditions include endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasia such as cancers of the prostate, breast and ovary, gonadotrophe pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome, benign prostatic hypertrophy, contraception and infertility (*e.g.*, assisted reproductive therapy such as *in vitro* fertilization). The compounds of this invention are also useful as an adjunct to treatment of growth hormone deficiency and short stature, and for the treatment of systemic lupus erythematosis. The compounds are also useful in combination with androgens, estrogens, progesterones, and antiestrogens and antiprogestogens for the treatment of endometriosis, fibroids, and in contraception, as well as in combination with an angiotensin-converting enzyme inhibitor, an angiotensin II-receptor antagonist, or a renin inhibitor for the treatment of uterine fibroids. In

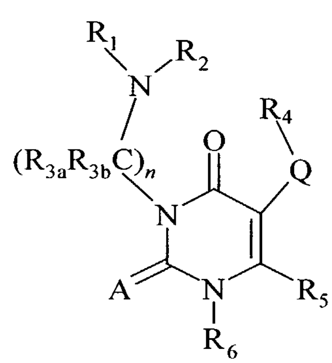
addition, the compounds may be used in combination with bisphosphonates and other agents for the treatment and/or prevention of disturbances of calcium, phosphate and bone metabolism, and in combination with estrogens, progesterones and/or androgens for the prevention or treatment of bone loss or hypogonadal symptoms such as hot flashes during therapy with a GnRH antagonist.

The methods of this invention include administering an effective amount of a GnRH receptor antagonist, preferably in the form of a pharmaceutical composition, to a mammal in need thereof. Thus, in still a further embodiment, pharmaceutical compositions are disclosed containing one or more GnRH receptor antagonists of this invention in combination with a pharmaceutically acceptable carrier and/or diluent.

These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information, procedures, compounds and/or compositions, and are each hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the present invention is directed generally to compounds useful as gonadotropin-releasing hormone (GnRH) receptor antagonists. The compounds of this invention have the following structure (I):



(I)

including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof,

wherein:

Q is a direct bond or $-(CR_{8a}R_{8b})_r-Z-(CR_{10a}R_{10b})_s-$;

A is O, S, or NR_7;

r and *s* are the same or different and independently 0, 1, 2, 3, 4, 5 or 6;

n is 2, 3 or 4;

Z is a direct bond or -O-, -S-, $-NR_9-$, -SO-, $-SO_2-$, $-OSO_2-$, $-SO_2O-$, $-SO_2NR_9-$, $-NR_9SO_2-$, -CO-, -COO-, -OCO-, $-CONR_9-$, $-NR_9CO-$, $-NR_9CONR_{9a}$, $-OCONR_9-$ or $-NR_9COO-$;

R_1 and R_2 are the same or different and independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, $-C(R_{1a})(=NR_{1b})$ or $-C(NR_{1a}R_{1c})(=NR_{1b})$;

or R_1 and R_2 taken together with the nitrogen atom to which they are attached form a heterocycle ring or a substituted heterocycle ring;

R_{3a} and R_{3b} are the same or different and, at each occurrence, independently hydrogen, alkyl, substituted alkyl, alkoxy, alkylthio, alkylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, $-COOR_{14}$ or $-CONR_{14}R_{15}$;

or R_{3a} and R_{3b} taken together with the carbon atom to which they are attached form a homocyclic ring, substituted homocyclic ring, heterocyclic ring or substituted heterocyclic ring;

or R_{3a} and R_{3b} taken together form $=NR_{3c}$;

or R_{3a} and the carbon to which it is attached taken together with R_1 and the nitrogen to which it is attached form a heterocyclic ring or substituted heterocyclic ring;

R_4 is higher alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, $-COR_{11}$, $-COOR_{11}$, $-CONR_{12}R_{13}$, $-OR_{11}$, $-OCOR_{11}$, $-OSO_2R_{11}$, $-SR_{11}$, $-SO_2R_{11}$, $-NR_{12}R_{13}$, $-NR_{11}COR_{12}$, $-NR_{11}CONR_{12}R_{13}$, $-NR_{11}SO_2R_{12}$ or $-NR_{11}SO_2NR_{12}R_{13}$;

R_5 is hydrogen, halogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, alkoxy, alkylthio, alkylamino, cyano or

nitro;

R_6 is higher alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

R_7 is hydrogen, $-SO_2R_{11}$, cyano, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; and

R_{1a}, R_{1b}, R_{1c}, R_{3c}, R_{8a}, R_{8b}, R_9, R_{9a}, R_{10a}, R_{10b}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are the same or different and, at each occurrence, independently hydrogen, acyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl;

or R_{1a} and R_{1b}, R_{8a} and R_{8b}, R_{10a} and R_{10b}, R_{12} and R_{13}, or R_{14} and R_{15} taken together with the atom or atoms to which they are attached form a homocyclic ring, substituted homocyclic ring, heterocyclic ring or substituted heterocyclic ring.

As used herein, the above terms have the following meaning:

"Alkyl" means a straight chain or branched, noncyclic or cyclic, unsaturated or saturated aliphatic hydrocarbon containing from 1 to 10 carbon atoms, while the term "lower alkyl" has the same meaning as alkyl but contains from 1 to 6 carbon atoms. The term "higher alkyl" has the same meaning as alkyl but contains from 2 to 10 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like. Cyclic alkyls are also referred to herein as a "homocycles" or "homocyclic rings." Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an "alkenyl" or "alkynyl", respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched

alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-butynyl, and the like.

"Aryl" means an aromatic carbocyclic moiety such as phenyl or naphthyl.

"Arylalkyl" means an alkyl having at least one alkyl hydrogen atoms replaced with an aryl moiety, such as benzyl, -$(CH_2)_2$phenyl, -$(CH_2)_3$phenyl, -CH(phenyl)$_2$, and the like.

"Heteroaryl" means an aromatic heterocycle ring of 5- to 10 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and bicyclic ring systems. Representative heteroaryls are furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

"Heteroarylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl moiety, such as -CH_2pyridinyl, -CH_2pyrimidinyl, and the like.

"Heterocycle" (also referred to herein as a "heterocyclic ring") means a 4- to 7-membered monocyclic, or 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated, or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Thus, in addition to the heteroaryls listed above, heterocycles also include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl,

tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heterocyclealkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heterocycle, such as $-CH_2$morpholinyl, and the like.

"Homocycle" (also referred to herein as "homocyclic ring") means a saturated or unsaturated (but not aromatic) carbocyclic ring containing from 3-7 carbon atoms, such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclohexene, and the like.

The term "substituted" as used herein means any of the above groups (*i.e.,* alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, homocycle, heterocycle and/or heterocyclealkyl) wherein at least one hydrogen atom is replaced with a substituent. In the case of a keto substituent ("-C(=O)-") two hydrogen atoms are replaced. When substituted one or more of the above groups are substituted, "substituents" within the context of this invention include halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, alkyl, alkoxy, alkylthio, haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl, as well as $-NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aC(=O)NR_aNR_b$, $-NR_aC(=O)OR_b$ $-NR_aSO_2R_b$, $-C(=O)R_a$, $-C(=O)OR_a$, $-C(=O)NR_aR_b$, $-OC(=O)NR_aR_b$, $-OR_a$, $-SR_a$, $-SOR_a$, $-S(=O)_2R_a$, $-OS(=O)_2R_a$ and $-S(=O)_2OR_a$. In addition, the above substituents may be further substituted with one or more of the above substituents, such that the substituent substituted alky, substituted aryl, substituted arylalkyl, substituted heterocycle or substituted heterocyclealkyl. R_a and R_b in this context may be the same or different and independently hydrogen, alkyl, haloalkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl.

"Halogen" means fluoro, chloro, bromo and iodo.

"Haloalkyl" means an alkyl having at least one hydrogen atom replaced with halogen, such as trifluoromethyl and the like.

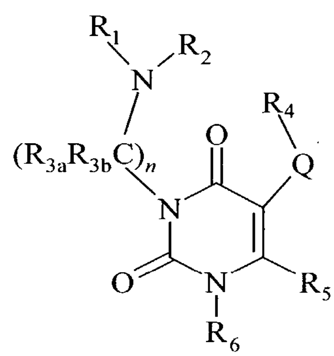
"Alkoxy" means an alkyl moiety attached through an oxygen bridge (*i.e.,* -O-alkyl) such as methoxy, ethoxy, and the like.

"Alkylthio" means an alkyl moiety attached through a sulfur bridge (*i.e.,* -S-alkyl) such as methylthio, ethylthio, and the like.

"Alkylsulfonyl" means an alkyl moiety attached through a sulfonyl bridge (*i.e.*, $-SO_2$-alkyl) such as methylsulfonyl, ethylsulfonyl, and the like.

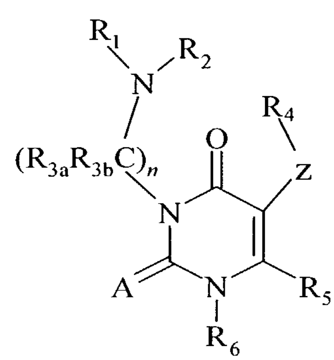
"Alkylamino" and "dialkylamino" mean one or two alkyl moiety attached through a nitrogen bridge (*i.e.*, -N-alkyl) such as methylamino, ethylamino, dimethylamino, diethylamino, and the like.

In one embodiment of this invention, A is O and representative GnRH receptor antagonists of this invention include compounds having the following structure (II):



(II)

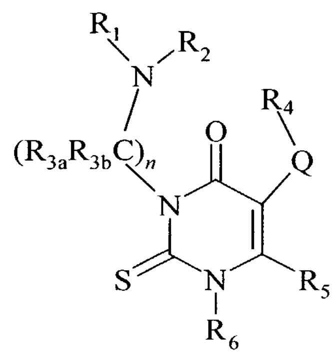
In another embodiment, Q is $-(CR_{8a}R_{8b})_r$-Z-$(CR_{10a}R_{10b})_s$-, r and s are both zero, and representative GnRH receptor antagonists of this invention include compounds having the following structure (III):



(III)

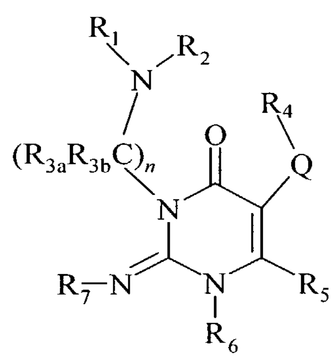
In another embodiment, A is S, as represented by the following structure

(IV):



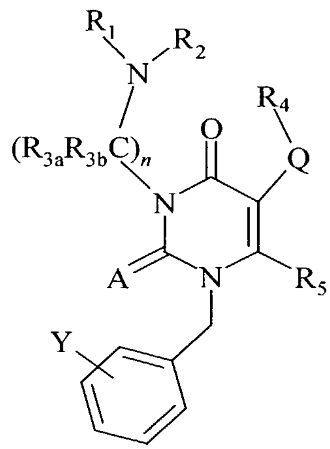
(IV)

Similarly, in another embodiment, A is NR_7, as represented by the following structure (V):



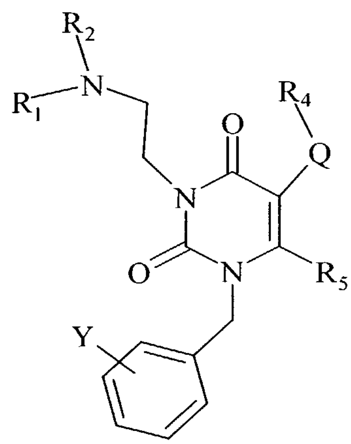
(V)

In further embodiments of this invention, R_6 is substituted or unsubstituted benzyl as represented by the following structure (VI) (wherein Y represents one or more optional substituents as defined above):



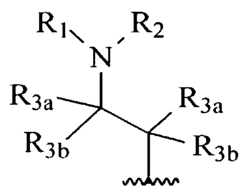
(VI)

In a more specific embodiment of structure (VI), A is O, n is 2, and each occurrence of R_{3a} and R_{3b} is H, as represented by the following structure (VII):

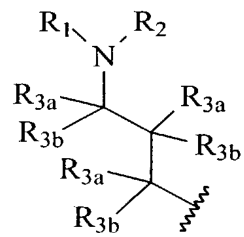


(VII)

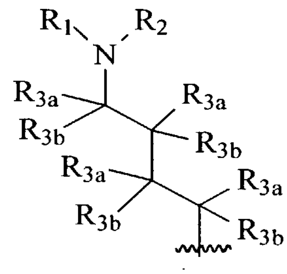
With regard to the "$R_1R_2N(CR_{3a}R_{3b})_n$-" moiety of structure (I), n may be 2, 3 or 4. Accordingly, this moiety may be represented by the following structure (i) when n is 2, structure (ii) when n is 3, and structure (iii) when n is 3:



(i)



(ii)

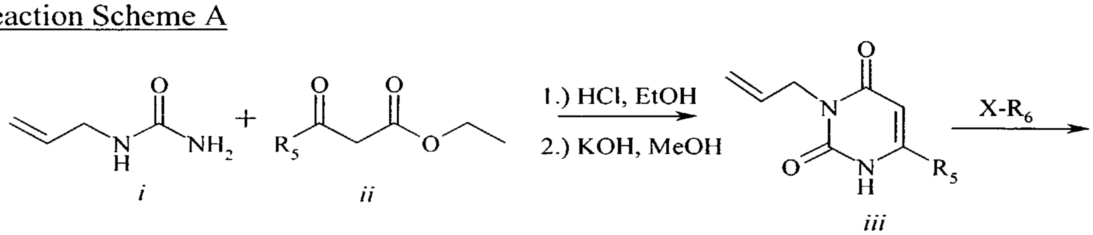


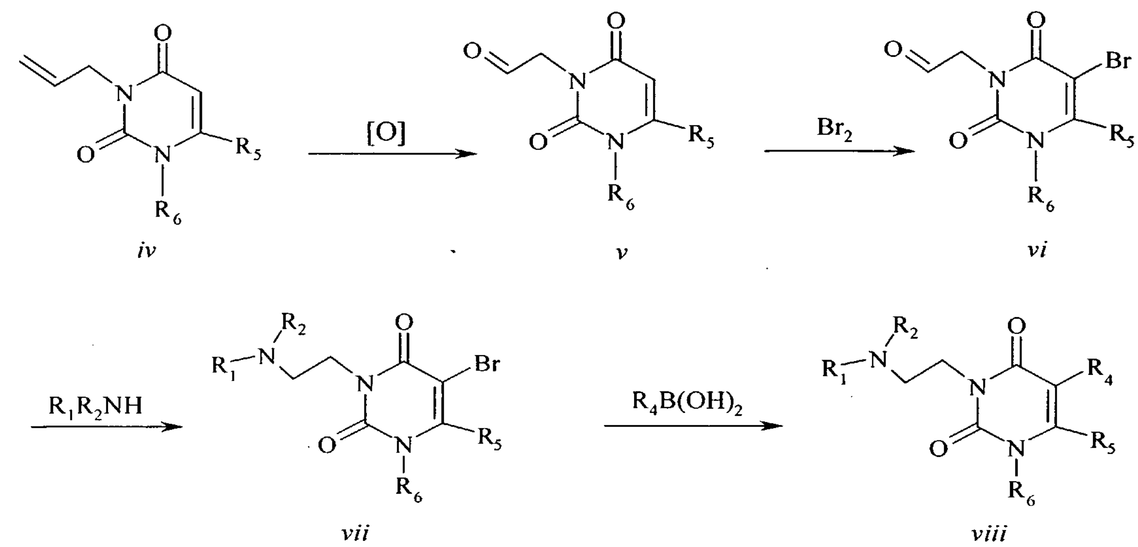
(iii)

wherein each occurrence of R_{3a} and R_{3b} above may be the same or different, and are as defined above. For example, when each occurrence of R_{3a} and R_{3b} in structures (i), (ii) and (iii) is hydrogen, the "$R_1R_2N(CR_{3a}R_{3b})_n$-" moiety has the structure $R_1R_2N(CH_2)_2$-, $R_1R_2N(CH_2)_3$- and $R_1R_2N(CH_2)_4$-, respectively.

The compounds of the present invention may be prepared by known organic synthesis techniques, including the methods described in more detail in the Examples. However in general, the compounds of structure (I) above may be made by the following Reaction Schemes. Specifically, compounds of structure (I) wherein A is oxygen may be made by Reaction Schemes A to E. Reaction Schemes F to K are appropriate for compounds of structure (I) wherein A is sulfur or NR_7, as well as where A is oxygen. Reaction Scheme L shows conditions for the conversion of thiouracils (where A is sulfur) to embodiments wherein A is NR_7. All substituents in the following Reaction Schemes are as defined above unless indicated otherwise.

Reaction Scheme A

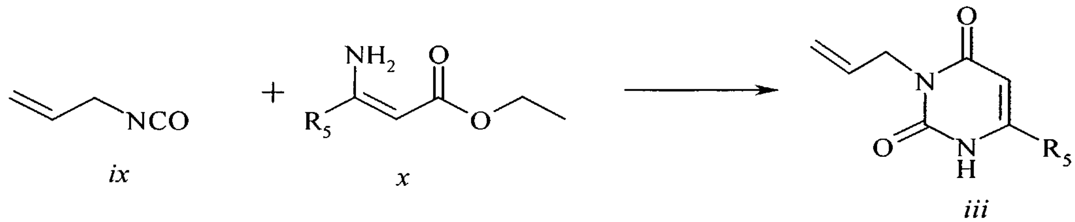




Allylurea (*i*) and substituted acetoacetate (ii) are condensed under acidic conditions in a solvent such as ethanol or DMF at 25 to 100°C and then cyclized under strongly basic conditions to give the substituted 3-allyl-2,4- pyrimidinedione (iii). Compound (iii) can then be modified by alkylation with an appropriate alkyl halide (where X is halogen) in a solvent such as DMF or ethanol for 1 hour to 2 days in the presence of a base such as sodium hydride or tetrabutylammonium fluoride to yield (iv). Oxidation of the allyl functionality, using osmium tetroxide and/or sodium periodate in solvent such as THF and/or water for 1-24 hours, gives aldehyde (v). Bromination of (v) using bromine or n-bromosuccinimide in a solvent such as acetic acid or chloroform for 1-24 hours resulted in brominated compound (vi). Reductive amination of (vi) with an appropriate amine using a reducing agent such as sodium triacetoxyborohydride in a solvent such as dichloroethane at 0 to 100°C for 1-24 hours gives (vii) which when coupled with an appropriate boronic acid in a solvent such as ethanol or toluene at 25 to 150°C for 1-24 hours in the presence of a Pd(0) catalyst gives (viii).

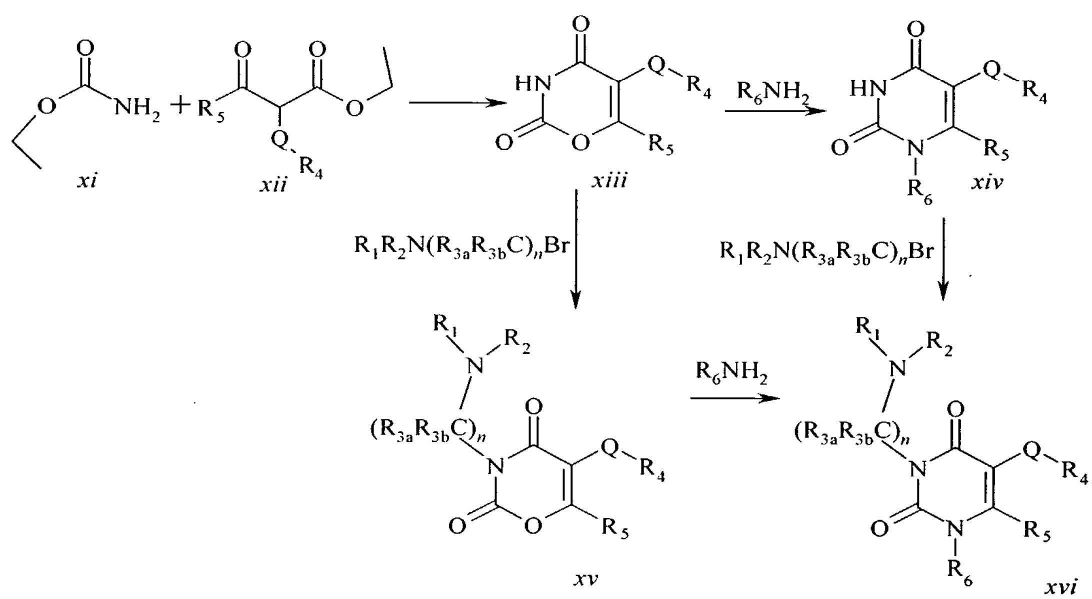
The final two steps of the above synthesis may also be reversed, the Suzuki coupling in that instance being the penultimate step and the reductive amination the final step. Alternatively, compound (iii) may be synthesized by the procedure in Example 2.

Reaction Scheme B



Compound (iii) from Reaction Scheme Al may also be synthesized by condensing and cyclizing allyl isocyanate (viii) and appropriate aminoalkene ester (ix) such as ethyl 3-aminocrotonate in a solvent such as toluene or DMF at 25 to 100°C for 1-24 hours.

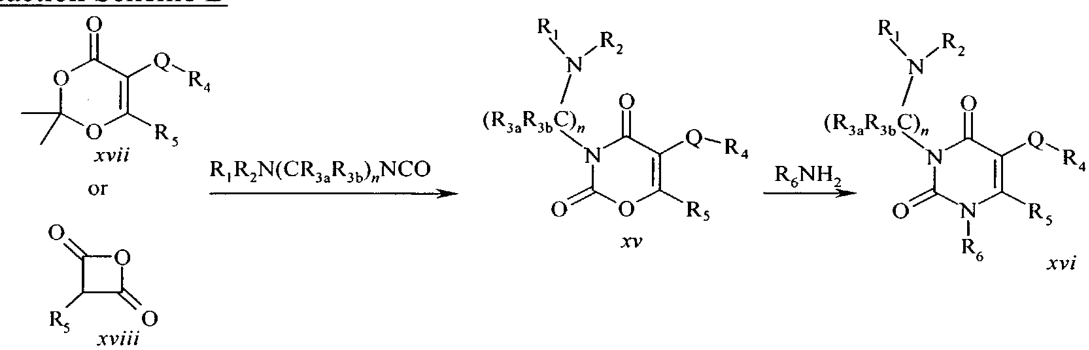
Reaction Scheme C



Cyclization of (xi) and (xii) in a solvent such as ethanol or DMF at 25 to 150°C for 1 to 24 hours gives oxazime (xiii). Amination of (xiii) in a solvent such as DMF or ethanol at 25 to 150°C for 1-24 hours yielded uracil derivative (xiv). Alkylation of (xiv) by an appropriate alkyl bromide in the presence of a base such as sodium hydride or sodium hydroxide in a solvent such as THF or DMF at 0 to 100°C for 1–24 hours gives substituted uracil (xvi). The order of the reaction scheme may be

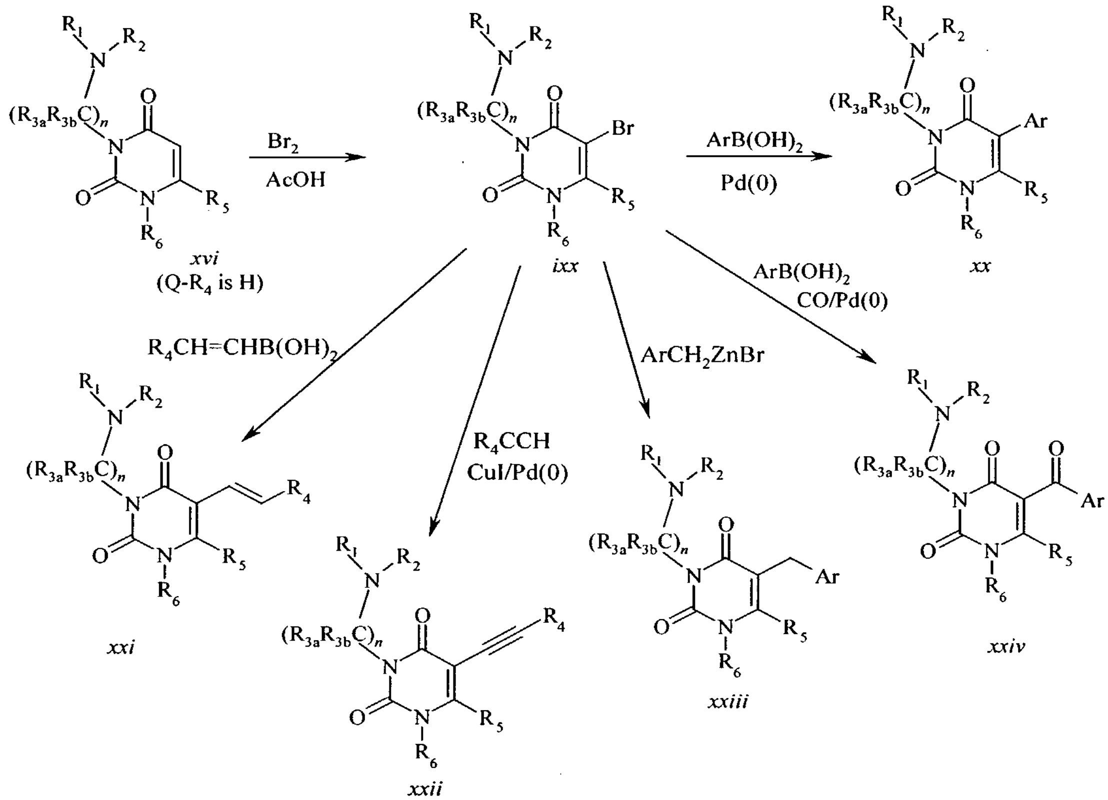
changed allowing oxazine (xiii) to first be alkylated under conditions above to (xv) followed by amination to the product (xvi).

Reaction Scheme D



Compound (*xvii*) or (*xviii*) react with an appropriately substituted isocyanate in a solvent such as toluene or chloroform at room temperature to 100°C for 1-24 hours as an alternative synthesis to intermediate oxazine (*xv*). Amination with a substituted amine in a solvent such as DMF or ethanol at a temperature of 25 to 100°C for a period of 1-24 hours results in product uracil (*xvi*).

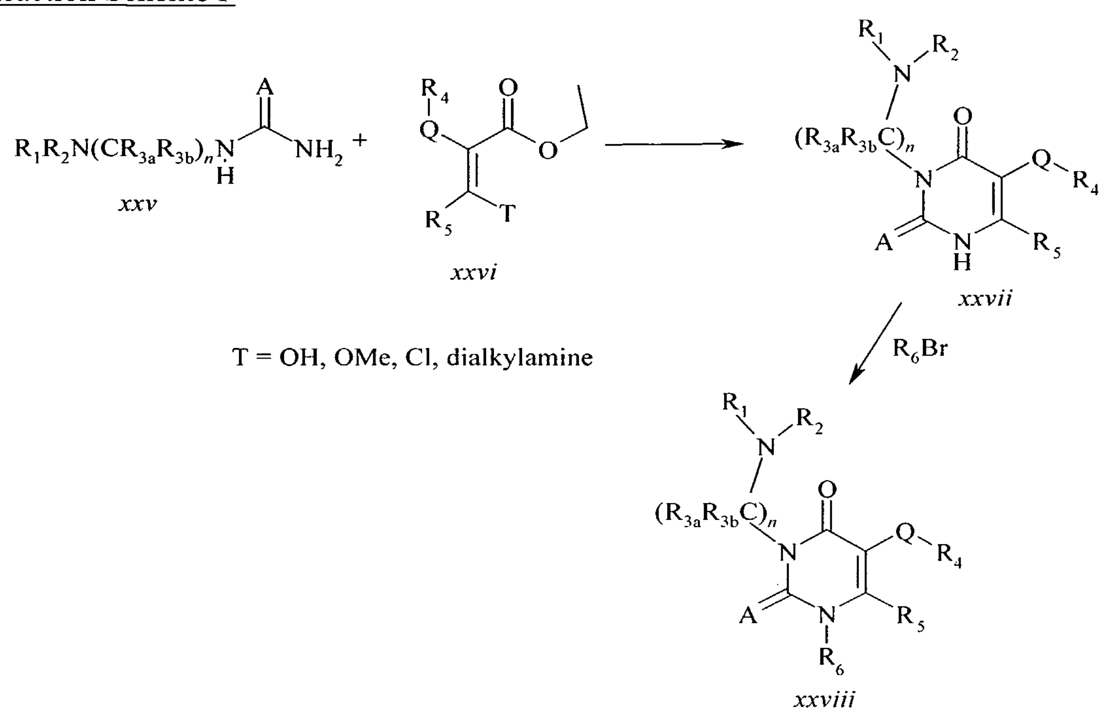
Reaction Scheme E



Intermediate (*xvi*) may be brominated using a brominating agent such as N-bromosuccinimide or bromine in a solvent such as acetic acid or chloroform at 0 to 100°C for a period of 1-24 hours to yield bromo compound (*ixx*). The bromo compound can undergo various palladium catalyzed cross coupling reactions. Compound (*ixx*) taken in solvent such as ethanol or THF under nitrogen atmosphere using an appropriate Pd(0) catalyst such as tetrakis(triphenylphosphine)Pd(0), may be reacted for 1–24 hours at 25 to 150°C with either an aryl boronic acid ($ArB(OH)_2$ where Ar is substituted aryl or heteroaryl) to yield product (*xx*) or with a substituted vinyl boronic acid to give compound (*xxi*). Compound (*ixx*) taken in solvent such as ethanol or THF using an appropriate Pd(0) catalyst in the presence of carbon monoxide and boronic acid yields (*xxiv*) after 1–24 hours at 0 to 150°C. Again using Pd(0) chemistry, compound (*xxiii*) is synthesized in a solvent such as THF or dioxane from the alkylation of (*ixx*) with an appropriate metal halide reagent for 1-24 hours at 0 to 150°C.

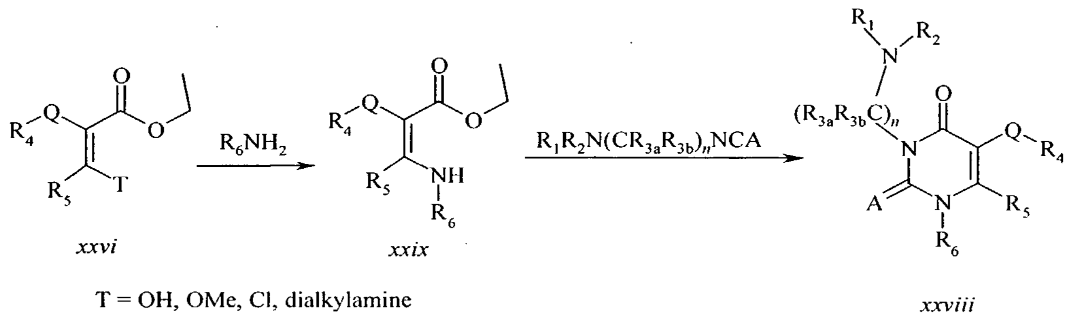
Compound (*ixx*) in the presence of a substituted acetylene, Pd(0) catalyst, metal halide such as CuI, and base such as triethylamine in an appropriate solvent such as acetonitrile or DMF at 25 to 150°C for 1-24 hours gives alkyne (*xxii*). Alkynyl uracil (*xxii*) may be selectively reduced to the alkene using a catalyst such as palladium/$BaSO_4$ under hydrogen atmosphere in solvent such as ethyl acetate or methanol to give (*xxi*).

<u>Reaction Scheme F</u>



Vinyl ester (*xxvi*) and (*xxv*) can be cyclized in a solvent such as DMF or EtOH at 25 to 150°C for 1-24 hours to give (*xxvii*). Alkylation of (*xxvii*) with an appropriate alkyl or aryl halide in a solvent such as DMF or THF in the presence of a base such as sodium hydride or sodium hydroxide for 1-24 hours at 0 to 150°C gives (*xxviii*).

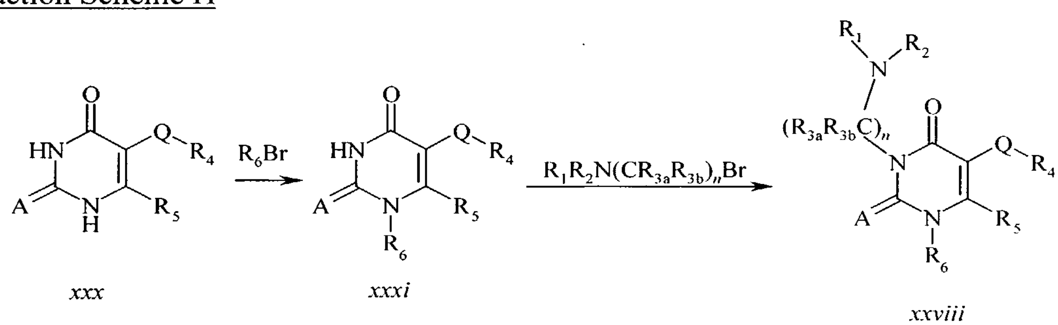
Reaction Scheme G



T = OH, OMe, Cl, dialkylamine

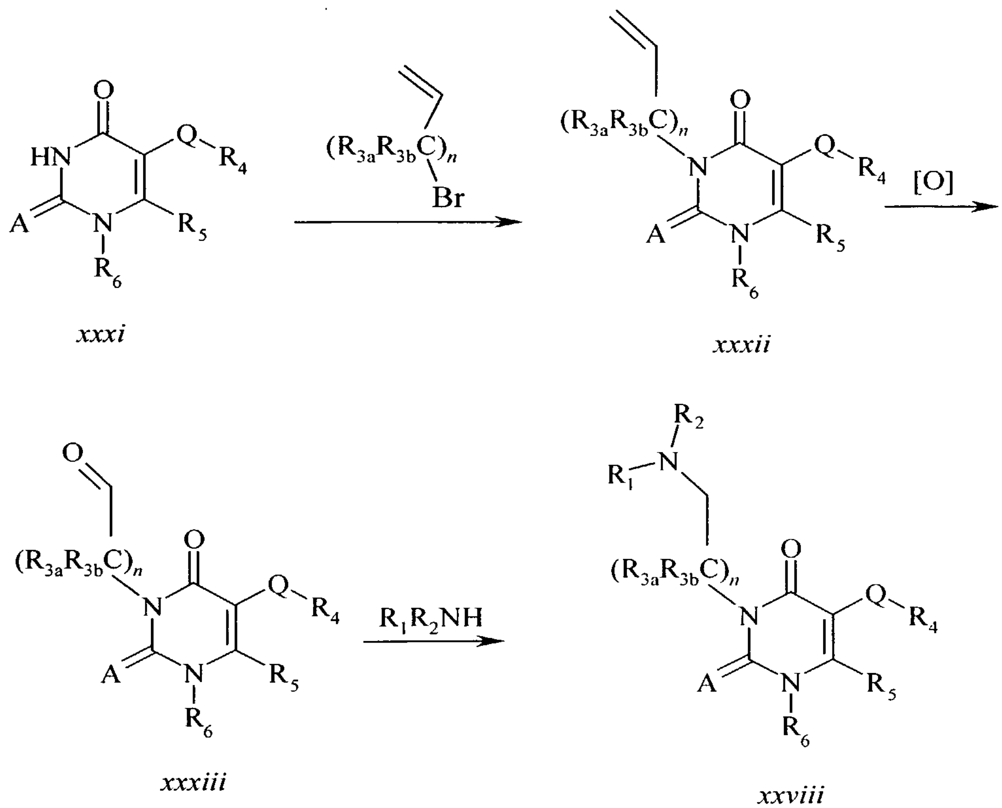
Vinyl ester (*xxvi*) can be condensed with a substituted amine in a solvent such as DMF or ethanol at 25 to 150°C for 1-24 hours to give (*xxix*). Cyclization of (*xxix*) with an isocyanate, isothiocyanate, or other appropriate compound in a solvent such as DMF, THF or dioxane, with or without a base such as sodium ethoxide or sodium hydride at 0 to 100°C for 1-24 hours gives product (*xxviii*).

Reaction Scheme H



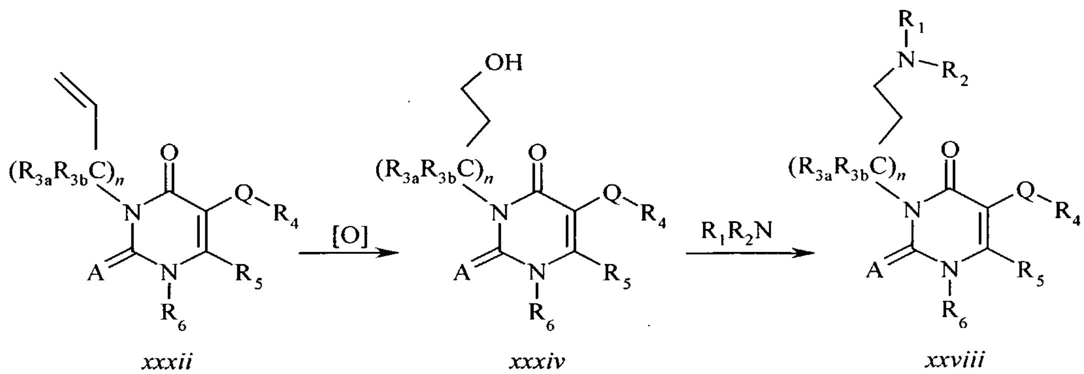
Compound (*xxx*) may be alkylated by an appropriate alkyl halide in the presence of a base such as sodium hydride or sodium hydroxide in a solvent such as THF or DMF at 0 to 50°C for 1 –24 hours to give (*xxxi*), which under further alkylation by a second alkyl halide gives product (*xxviii*).

Reaction Scheme I



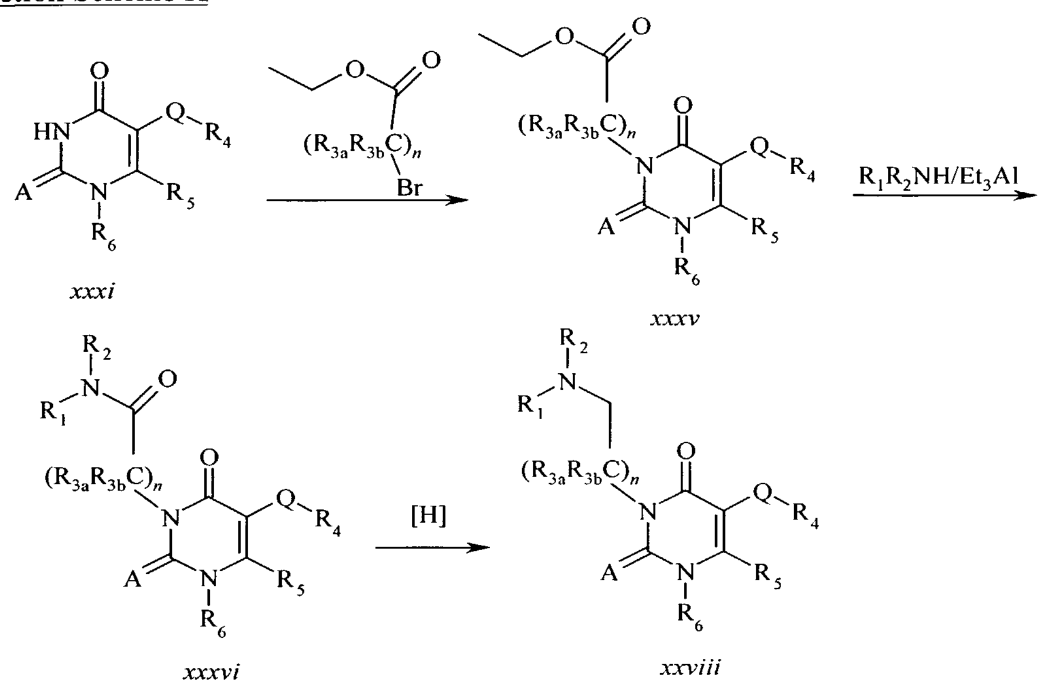
Compound (*xxxi*) may be alkylated by an appropriate alkyl halide in the presence of a base such as sodium hydride or sodium hydroxide in a solvent such as THF or DMF at 0 to 100°C for 1–24 hours to give (*xxxii*). The terminal double bond is oxidized using an appropriate oxidizing reagent such as osmium tetroxide or sodium periodate in solvent such as THF and/or water for 1-24 hours at 0 to 100°C to give aldehyde (*xxxiii*). Reductive amination of (*xxxiii*) with an appropriate amine using a reducing agent such as sodium cyanoborohydride in a solvent such as dichloroethane or acetonitrile at 0 to 100°C for 1-24 hours gives (*xxviii*).

Reaction Scheme J



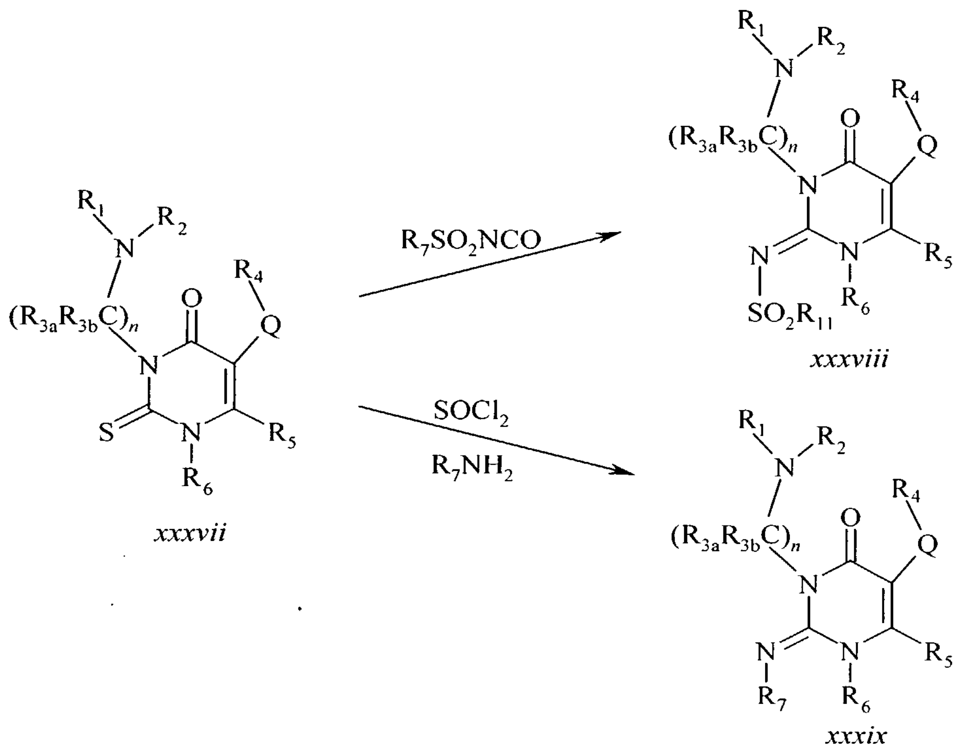
Compound (xxxii) can be oxidized to the alcohol (*xxxiv*) first by hydroboration with a borane complex in a solvent such as THF followed by oxidation with ozone or hydrogen peroxide in a solvent such as methanol, ethanol and/or water at -25 to 100°C for a period of 0.5-24 hours. Treatment of (*xxxiv*) with mesyl or tosyl chloride in methylene chloride with a base such as triethylamine or pyridine at 0 to 100°C for 1-24 hours followed by reaction with an amine in a solvent such as DMF or toluene for 0.5-12 hours at 25 to 100°C gives (*xxviii*).

Reaction Scheme K



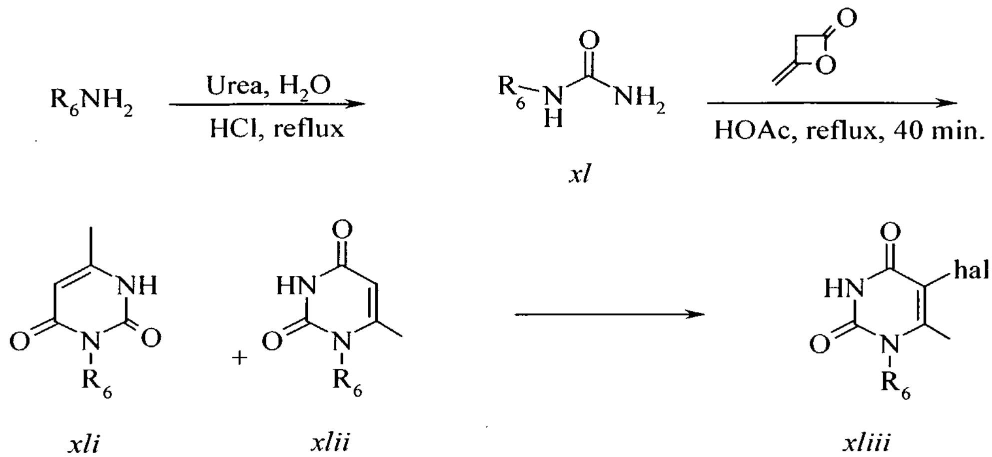
Compound (*xxxi*) can be alkylated with an appropriate ester in a solvent such as DMF or ethanol in the presence of a base such as sodium hydride or sodium ethoxide at a temperature of 25 to 150°C for a period of 1-24 hours to give (*xxxv*). Ester (*xxxv*) in a solvent such as chloroform or benzene with substituted amine and Lewis acid such as triethylaluminum gives amide (*xxxvi*) after 1-24 hours at 0 to 100°C. Reduction of (*xxxvi*) with lithium aluminum hydride or borane complex in a solvent such as THF or ether at 0 to 100°C for 1-12 hours gives product (*xxviii*).

Reaction Scheme L



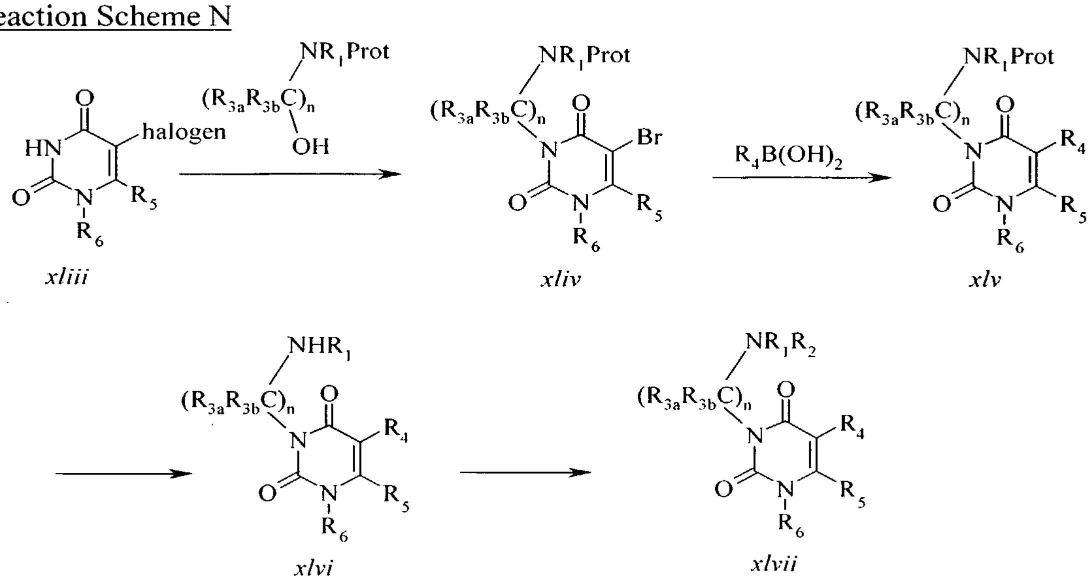
Thiouracil compound (*xxxvii*) in the presence of a substituted sulfonylisocyanate in a solvent such as benzene or toluene for 1-48 hours at 25 to 125°C gives sulfonamide (*xxxviii*). Thiouracil (*xxxvii*) chlorinated by thionyl chloride or phosphorous oxychloride at -25 to 100°C for 1-24 hours followed by amination with an appropriate amine in a solvent such as benzene or toluene at 25 to 150°C for 1-24 hours gives compound (*xxxix*).

Reaction Scheme M



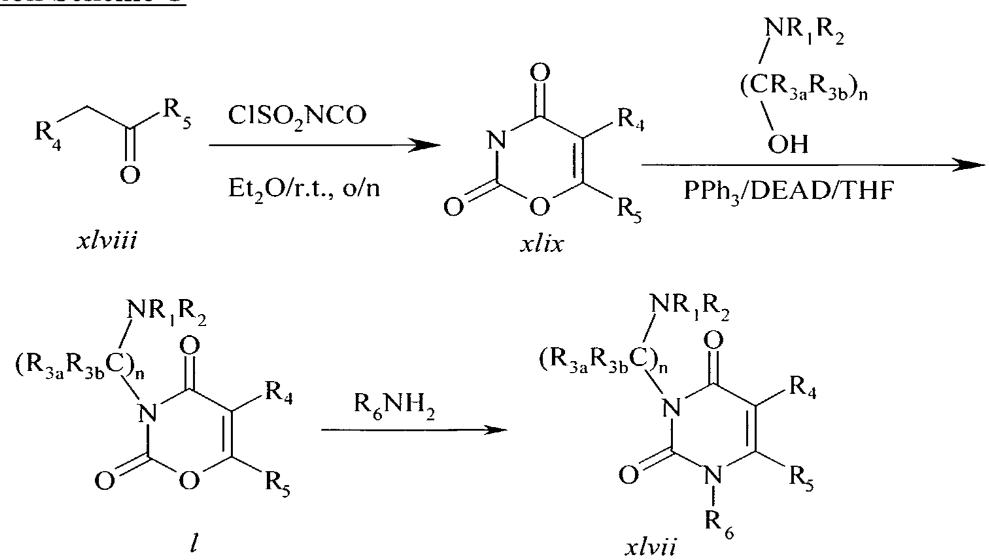
Substituted amine in the presence of urea or thiourea is heated at a temperature of 50 –125 °C for 0.5 to 12 hours to give (*xl*). Cyclization of (*xl*) with diketene at 50 – 150 °C in acidic media such as acetic or formic acid for 5 minutes to 4 hours gives a mixture of isomers (*xli*) and (*xlii*). Halogenation of (*xlii*) using a halogenating reagent such as N-halosuccinimide in chloroform or bromine in acetic acid for 5 minutes to 24 hours gives halogenated product (*xliii*).

Reaction Scheme N



Uracil compound (*xliii*) and an appropriately substituted alcohol are condensed under Mitsonobu conditions such as diethyl or dibutyl axodicarboxylate and triphenylphosphine in a solvent such as THF at 0 – 100 °C for 0.5 to 10 hours to give compound (*xliv*). A Suzuki coupling of (*xliv*) and a boronic acid or boronic acid ester in a solvent such as ethanol or toluene at 25 to 150°C for 1-24 hours in the presence of a Pd(0) catalyst gives (*xlv*). Deprotection of the protected amine gives (*xlvi*). Reductive amination of (*xlvi*) with an appropriate aldehyde in a solvent such as methylene chloride or acetonitrile using a reducing agent such as sodium triacetoxyborohydride or sodium borohydride at 0 to 100 °C for 1-24 hours gives (*xlvii*).

Reaction Scheme O



Keto or aldehyde *xlviii* in the presence of chlorosulfonylisocyanate or chlorocarbonylisocyanate yields oxaz-2,4-dione *xlix* after stirring for 1-24 hours at 0 °C to 75 °C in a solvent such as THF or ether. Mitsonobu condensation with an appropriate alcohol gives *l* which when in the presence of amine R_6NH_2 at room temperature to 125 °C, with or without solvent such as DMF or catalyst such as acetic or hydrochloric acid, for ½ to 24 hours gives *xlvii*.

The compounds of the present invention may generally be utilized as the free acid or free base. Alternatively, the compounds of this invention may be used in

the form of acid or base addition salts. Acid addition salts of the free amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, trifluoroacetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Base addition salts included those salts that form with the carboxylate anion and include salts formed with organic and inorganic cations such as those chosen from the alkali and alkaline earth metals (for example, lithium, sodium, potassium, magnesium, barium and calcium), as well as the ammonium ion and substituted derivatives thereof (for example, dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, and the like). Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all acceptable salt forms.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) *in vivo* when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol and amine functional groups of the compounds of structure (I). Further, in the case of a carboxylic acid (-COOH), esters may be employed, such as methyl esters, ethyl esters, and the like.

With regard to stereoisomers, the compounds of structure (I) may have chiral centers and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof. Compounds of structure (I) may also possess

axial chirality which may result in atropisomers. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the present invention. In addition, some of the compounds of structure (I) may also form solvates with water or other organic solvents. Such solvates are similarly included within the scope of this invention.

The effectiveness of a compound as a GnRH receptor antagonist may be determined by various assay methods. Suitable GnRH antagonists of this invention are capable of inhibiting the specific binding of GnRH to its receptor and antagonizing activities associated with GnRH. For example, inhibition of GnRH stimulated LH release in immature rats may be measured according to the method of Vilchez-Martinez (*Endocrinology 96*:1130-1134, 1975). Briefly, twenty-five day old male Sprague-Dawley rats are administered an GnRH antagonist in saline or other suitable formulation by oral gavage, sub-cutaneous injection, or intravenous injection. This is followed by sub-cutaneous injection of 200 ng GnRH in 0.2 ml saline. Thirty minutes after the last injection, the animals are decapitated and trunk blood collected. After centrifugation, the separated plasma is stored at –20 °C until determination of the LH and FSH by radioimmunoassay. Other techniques for determining the activity of GnRH receptor antagonists are well known in the field, such as the use of cultured pituitary cells for measuring GnRH activity (Vale et al., *Endocrinology 91*:562-572, 1972), and a technique for measuring radioligand binding to rat pituitary membranes (Perrin et al., *Mol. Pharmacol. 23*:44-51, 1983).

For example, effectiveness of a compound as a GnRH receptor antagonist may be determined by one or more of the following assays.

<u>Rat Anterior Pituitary Cell Culture Assay of GnRH Antagonists</u>

Anterior pituitary glands are collected from 7-week-old female Sprague-Dawley rats and the harvested glands digested with collagenase in a dispersion flask for 1.5 hr at 37°C. After collagenase digestion, the glands are further digested with neuraminidase for 9 min at 37°C. The digested tissue is then washed with 0.1% BSA/McCoy's 5A medium, and the washed cells suspended in 3% FBS/0.1

BSA/McCoy's 5A medium and plated into 96-well tissue culture plates at a cell density of 40,000 cells per well in 200 μl medium. The cells are then incubated at 37°C for 3 days. One pituitary gland normally yields one 96-well plate of cells, which can be used for assaying three compounds. For assay of an GnRH antagonist, the incubated cells are first washed with 0.1% BSA/McCoy's 5A medium once, followed by addition of the test sample plus 1nM GnRH in 200 μl 0.1% BSA/McCoy's 5A medium in triplicate wells. Each sample is assayed at 5-dose levels to generate a dose-response curve for determination of its potency on the inhibition of GnRH stimulated LH and/or FSH release. After 4-hr incubation at 37°C, the medium is harvested and the level of LH and/or FSH secreted into the medium determined by RIA.

RIA of LH and FSH

For determination of the LH levels, each sample medium is assayed in duplicates and all dilutions are done with RIA buffer (0.01M sodium phosphate buffer/0.15M NaCl/1% BSA/0.01% NaN3, pH 7.5) and the assay kit is obtained from the Nation Hormone and Pituitary Program supported by NIDDK. To a 12x75 mm polyethylene test tube is added 100 μl of sample medium diluted 1:5 or rLH standard in RIA buffer and 100 μl of [125I]-labeled rLH (~30,000 cpm) plus 100 μl of rabbit anti-rLH antibody diluted 1:187,500 and 100 μl RIA buffer. The mixture is incubated at room temperature over-night. In the next day, 100 μl of goat anti-rabbit IgG diluted 1:20 and 100 μl of normal rabbit serum diluted 1:1000 are added and the mixture incubated for another 3 hr at room temperature. The incubated tubes are then centrifuged at 3,000 rpm for 30 min and the supernatant removed by suction. The remaining pellet in the tubes is counted in a gamma-counter. RIA of FSH is done in a similar fashion as the assay for LH with substitution of the LH antibody by the FSH antibody diluted 1:30,000 and the labeled rLH by the labeled rFSH.

Radio-iodination of GnRH peptide

The GnRH analog is labeled by the chloramine-T method. To 10 μg of peptide in 20 μl of 0.5M sodium phosphate buffer, pH 7.6, is added 1 mCi of Na125I,

followed by 22.5 μg chloramine-T and the mixture vortexed for 20 sec. The reaction is stopped by the addition of 60 μg sodium metabisulfite and the free iodine is removed by passing the iodinated mixture through a C-8 Sep-Pak cartridge (Millipore Corp., Milford, MA). The peptide is eluted with a small volume of 80% acetonitrile/water. The recovered labeled peptide is further purified by reverse phase HPLC on a Vydac C-18 analytical column (The Separations Group, Hesperia, CA) on a Beckman 334 gradient HPLC system using a gradient of acetonitrile in 0.1% TFA. The purified radioactive peptide is stored in 0.1% BSA/20% acetonitrile/0.1% TFA at -80°C and can be used for up to 4 weeks.

<u>GnRH receptor membrane binding assay</u>

Cells stably, or transiently, transfected with GnRH receptor expression vectors are harvested, resuspended in 5% sucrose and homogenized using a polytron homogenizer (2x15 sec). Nucleii are removed by centrifugation (3000 x g for 5 min.), and the supernatant centrifuged (20,000 x g for 30 min, 4 °C) to collect the membrane fraction. The final membrane preparation is resuspended in binding buffer (10mM Hepes (pH 7.5), 150 mM NaCl, and 0.1% BSA) and stored at –70 °C. Binding reactions are performed in a Millipore MultiScreen 96-well filtration plate assembly with polyethylenimine coated GF/C membranes. The reaction is initiated by adding membranes (40 ug protein in 130 ul binding buffer) to 50ul of [^{125}I]-labeled GnRH peptide (~100,000 cpm), and 20ul of competitor at varying concentrations. The reaction is terminated after 90 minutes by application of vacuum and washing (2X) with phosphate buffered saline. Bound radioactivity is measured using 96-well scintillation counting (Packard Topcount) or by removing the filters from the plate and direct gamma counting. K_i values are calculated from competition binding data using non-linear least squares regression using the Prism software package (GraphPad Software).

Activity of GnRH receptor antagonists are typically calculated from the IC_{50} as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the GnRH receptor, and is reported as a "K_i" value calculated by the following equation:

$$K_i = \frac{IC_{50}}{1 + L / K_D}$$

where L = radioligand and K_D = affinity of radioligand for receptor (Cheng and Prusoff, *Biochem. Pharmacol. 22*:3099, 1973). GnRH receptor antagonists of this invention have a K_i of 100 μM or less. In a preferred embodiment of this invention, the GnRH receptor antagonists have a K_i of less than 10 μM, and more preferably less than 1μM, and even more preferably less than 0.1 μM (*i.e.*, 100 nM). To this end, representative GnRH receptor antagonists of this invention which have a K_i of less than 100 nMwhen using the GnRH receptor membrane binding assay as described above include the following Compound Nos.

Table No.	Compound No.
1	3, 10, 11, 12, 13
3	1, 4
6	1, 2, 3, 8
7	2, 3, 4, 7, 9, 10, 11
8	2, 3, 4, 7, 12, 13, 14, 15, 16, 17, 19-21, 23, 25, 27-29, 31-36, 38-39, 42, 44, 51, 58, 59, 61, 63-66, 68, 70, 75, 77-97, 100, 106, 107, 109-113, 115-117, 124-135, 137-140
9	3, 4, 6, 7, 10, 14-16, 19, 24, 26, 32, 35, 37, 39, 40, 42, 46-49, 51-53, 55, 56, 58, 61, 63, 64, 66-68, 70, 72-78, 80-82, 85, 86, 89-93, 95, 96, 98-102, 107, 109, 110, 112, 138, 140, 142, 143, 145, 146, 149, 151-155, 157-162, 164, 166-168, 170-176, 178-188, 191, 194-197, 199, 200, 202-207, 210-212, 214, 215, 219, 224, 225, 227, 229, 232-234, 237, 240, 242, 244, 245, 247, 249, 251-256, 258-261, 263, 265-267, 270, 275, 277-279, 281, 286, 287, 295-301, 304, 305, 307-309, 312, 318, 320, 321, 325-329, 331-336, 338-346, 348-355, 357-359, 361, 362, 364-385, 387-397, 399, 402, 406, 409, 410, 413, 415, 417, 419-424, 427-434, 437-439, 441, 443, 446, 448, 454, 455, 470, 473, 477, 480-487, 490-493, 495, 502, 503, 509, 512, 514, 517, 519-524, 547-552, 554-560, 565-568, 570, 581-584, 589, 595, 596, 602, 606-609, 612, 613, 618, 621, 622, 624-627, 634, 636, 642-648, 652, 653, 655-658, 660-662, 664, 665, 668-672, 677, 678, 680, 681, 688, 694, 696, 698-702, 704, 706-708, 711, 712, 714, 718-726, 729-741, 745, 747-750, 755-756, 759-763, 774
10	1, 10, 14, 21-23, 25, 52, 54-56, 60, 61, 64, 65
12	1, 4, 5, 10, 20-22, 24, 27, 32
13	2, 4

15	1, 2

As mentioned above, the GnRH receptor antagonists of this invention have utility over a wide range of therapeutic applications, and may be used to treat a variety of sex-hormone related conditions in both men and women, as well as mammals in general. For example, such conditions include endometriosis, uterine fibroids, polycystic ovarian disease, hirsutism, precocious puberty, gonadal steroid-dependent neoplasia such as cancers of the prostate, breast and ovary, gonadotrophe pituitary adenomas, sleep apnea, irritable bowel syndrome, premenstrual syndrome, benign prostatic hypertrophy, contraception and infertility (*e.g.*, assisted reproductive therapy such as *in vitro* fertilization).

The compounds of this invention are also useful as an adjunct to treatment of growth hormone deficiency and short stature, and for the treatment of systemic lupus erythematosis.

In addition, the compounds are useful in combination with androgens, estrogens, progesterones, and antiestrogens and antiprogestogens for the treatment of endometriosis, fibroids, and in contraception, as well as in combination with an angiotensin-converting enzyme inhibitor, an angiotensin II-receptor antagonist, or a renin inhibitor for the treatment of uterine fibroids. The compounds may also be used in combination with bisphosphonates and other agents for the treatment and/or prevention of disturbances of calcium, phosphate and bone metabolism, and in combination with estrogens, progesterones and/or androgens for the prevention or treatment of bone loss or hypogonadal symptoms such as hot flashes during therapy with a GnRH antagonist.

In another embodiment of the invention, pharmaceutical compositions containing one or more GnRH receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a GnRH receptor antagonist of the present invention and a pharmaceutically acceptable carrier and/or diluent. The GnRH receptor antagonist is present in the

composition in an amount which is effective to treat a particular disorder--that is, in an amount sufficient to achieve GnRH receptor antagonist activity, and preferably with acceptable toxicity to the patient. Typically, the pharmaceutical compositions of the present invention may include a GnRH receptor antagonist in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more typically from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a GnRH receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the GnRH receptor antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, PA 1990.

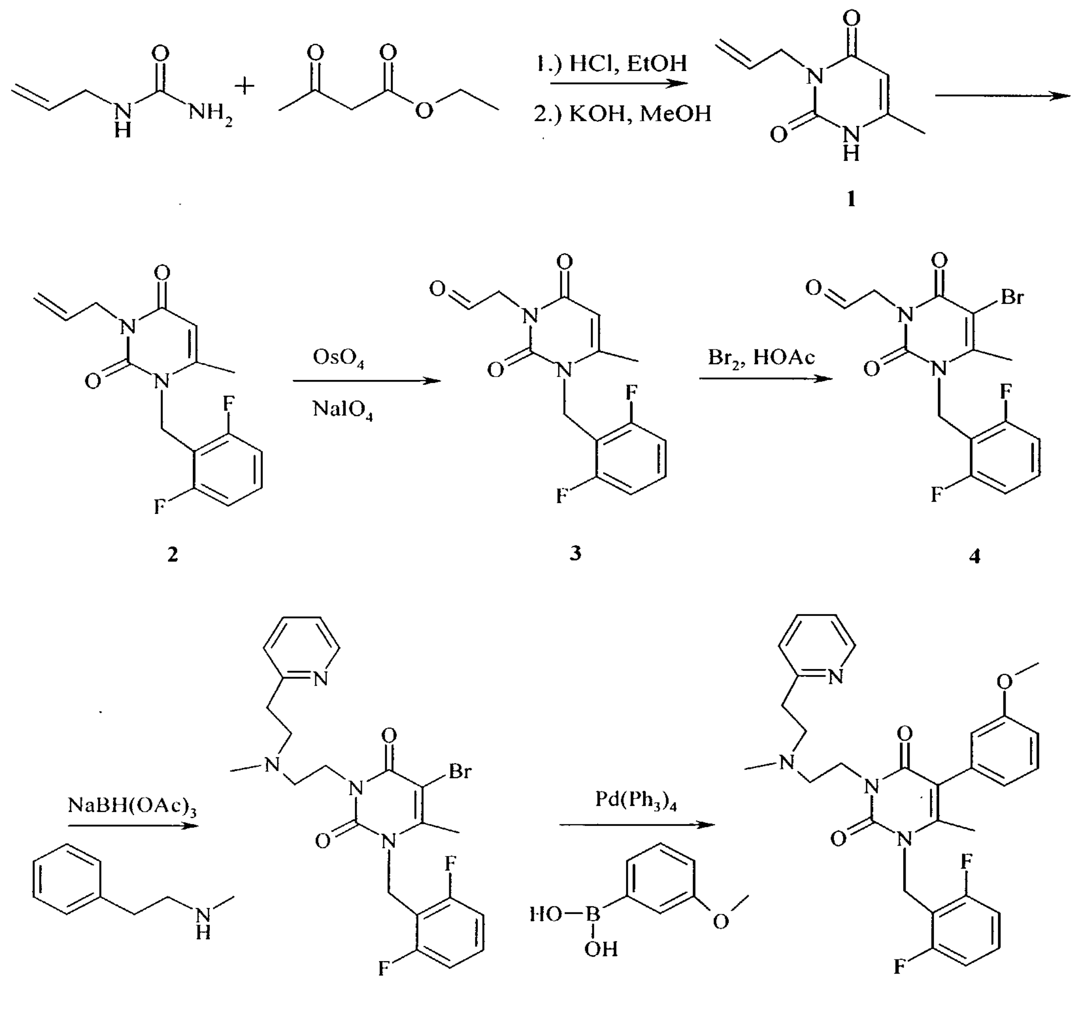
In another embodiment, the present invention provides a method for treating sex-hormone related conditions as discussed above. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the condition. In this context, "treat" includes prophylactic administration. Such methods include systemic administration of a GnRH receptor antagonist of this invention, preferably in the form of a pharmaceutical composition as discussed above. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of GnRH receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous

injection solutions which may contain, in addition to the GnRH receptor antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

The following example is provided for purposes of illustration, not limitation. In summary, the GnRH receptor antagonists of this invention may be assayed by the general methods disclosed above, while the following Examples disclose the synthesis of representative compounds of this invention.

EXAMPLE 1

SYNTHESIS OF 1-(2,6-DIFLUOROBENZYL)-5-(3-METHOXYPHENYL)-6-METHYL-3-[N-METHYL-N-(2-PYRIDYLETHYL)AMINOETHYL]URACIL



Step 1A 3-Allyl-6-methyluracil

To allylurea (25 g, .25 mol) in ethanol (10 mL) was added ethyl acetoacetate (31.86 mL, .25 mol) and 10 drops conc. HCl. After 12 days at room temperature, concentration gave an oil which was dissolved in MeOH. KOH (22.5 g, 0.34 mol) was added and the solution refluxed for 1 hour. After neutralization, the

resulting solid *1* was collected. Yield 2.7 g (7%). NMR ($CDCl_3$) δ: 2.16 (3H, s), 4.52 (2H, d), 5.18 (1H, d), 5.23 (1H, d), 5.60 (1H, s), 5.82-5.93 (1H, m), 10.3 (1H, s).

Step 1B 3-Allyl-1-(2,6-difluorobenzyl)-6-methyluracil

To *1* (2.6 g, 15.7 mmol) in DMF (20 mL) was added tetrabutylammoniumfluoride (25 mmol) and 2,6-difluorobenzyl bromide (4.14 g, 20 mmol). After 2 days stirring at room temperature, column chromatography using ethyl acetate/ hexane gave 2.7 g (59% yield) of *2*. MS 293 $(MH)^+$.

Step 1C 3-Acetaldehyde-1-(2,6-difluorobenzyl)-6-methyluracil

To a solution of *2* (1.46 g, 5 mmol) in THF (20 mL) and H_2O (10 mL) was added osmium tetroxide (200 mg) and $NaIO_4$ (3.2 g, 15 mmol). After 2 hr, another 1 g of $NaIO_4$ was added. Ethyl acetate and H_2O were added and the layers separated. Evaporation of the organic layer gave *3* as a crude solid (1.0 g, 68%). MS 295 $(MH)^+$.

Step 1D 3-Acetaldehyde-5-bromo-1-(2,6-difluorobenzyl)-6-methyluracil

3 (294 mg, 1 mmol) was dissolved in acetic acid and bromine (1.2 eq) was added. The reaction mixture was stirred at room temperature for 1 hr, evaporated and the residue was dissolved in EtOAc, washed with 1N KOH solution and concentrated to give *4* as a crude oil (295 mg, 79%). MS 373/375 $(MH)^+$. NMR ($CDCl_3$) δ: 2.55 (3H, s), 4.87 (2H, d), 5.33 (2H, s), 7.26-7.33 (3H, 2m), 9.59 (1h, d).

Step 1E 5-Bromo-1-(2,6-difluorobenzyl)-6-methyl-3-[N-methyl-N-(2-pyridylethyl)aminoethyl]uracil

To *4* (295 mg, 0.8 mmol) in dichloroethane was added 2-(methylaminoethyl)pyridine (200 mg, 1.5 mmol) and $NaBH(OAc)_3$ (636 mg, 3mmol). After overnight stirring, the reaction mixture was concentrated, dissolved in EtOAc, washed with H_2O, and purified by prep TLC to give 190 mg of *5* (48%).

Step 1F <u>1-(2,6-Difluorobenzyl)-5-(3-methoxyphenyl)-6-methyl-3-[N-methyl-N-(2-pyridylethyl)aminoethyl]uracil ("Cpd. No. 1")</u>

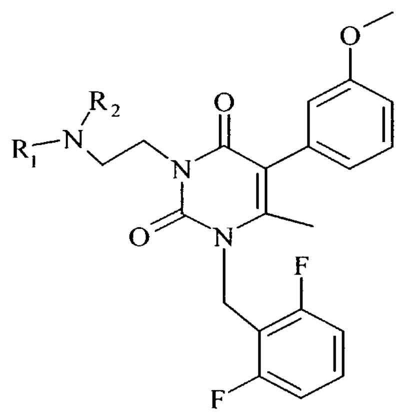
5 (150 mg, 0.3 mmol), 3-methoxyphenylboronic acid (92 mg, 0.6 mmol), K_2CO_3 (100 mg, 0.72 mmol), and $Pd(PPh_3)_4$ (20 mg) in H_2O (5 mL) and toluene (10 mL) was heated in a sealed tube at 100 °C for 12 hr. Purification by HPLC gave 40 mg of ***6*** ("Cpd. No. 1") as the TFA salt (21% yield). MS 521 $(MH)^+$ NMR ($CDCl_3$) δ: 2.14 (3H, s), 3.02 (3H, s), 3.50 (2H, m), 3.63 (2H, m), 3.71 (2H, m), 3.81 (3H, s), 4.37 (2H, m), 5.25 (2H, s), 6.81-6.83 (2H, m), 6.88-6.95 (3H, m), 7.28-7.34 (2H, m), 7.63 (1H, m), 7.89 (1H, d), 8.13 (1H, t), 8.62 (1H, br s).

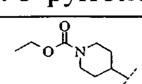
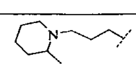
EXAMPLE 2

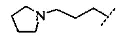
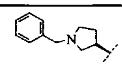
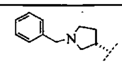
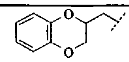
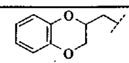
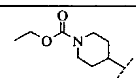
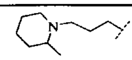
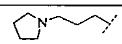
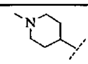
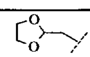
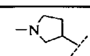
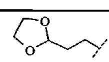
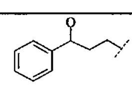
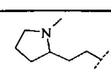
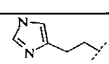
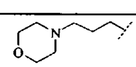
REPRESENTATIVE COMPOUNDS

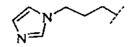
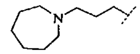
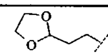
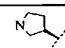
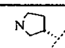
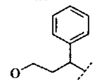
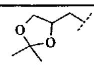
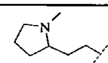
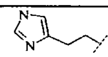
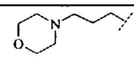
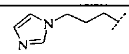
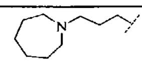
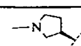
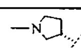
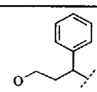
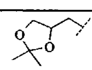
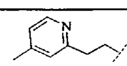
Following the procedures as set forth in Example 1 above, the compounds of the following Table 1 were prepared.

Table 1



Cpd. No.	R_1	R_2	MS $(MH)^+$
1-1	2-$PyCH_2CH_2$	H	507
1-2	2-$PyCH_2$	H	493
1-3	2-$PyCH_2$	Me	507
1-4	Bz	Me	506
1-5	$PhCH_2CH_2$	Me	520
1-6	2-$PyCH_2CH_2$	Pr	549
1-7	$PhCHCH_3$	Me	520
1-8	$PhCHCH_3$	Me	520
1-9	Bz	$(CH_3)_2N(CH_2)_2$	563
1-10	2-$PyCH_2CH_2$	Et	535
1-11	2-(6-Cl-Py)CH_2CH_2	Me	416, 555
1-12	2-$PyCH_2CH_2$	CyclopropylCH_2	561
1-13	1-Et-3-pyrrolidinyl	Et	527
1-14		H	557
1-15		H	541
1-16	$(CH_3)_2CHOCH_2CH_2CH_2$	H	502
1-17	$Et_2NCH_2CH_2$	Me	515

1-18		H	513
1-19	$CH_3OCH_2CH_2CH_2$	H	474
1-20	$(EtO)_2CHCH_2CH_2$	H	532
1-21	$CH_3OCH_2CH_2$	Me	474
1-22		Me	575
1-23		Me	575
1-24		H	550
1-25	$CH_3OCH_2CH_2CH_2$	Me	488
1-26	$(EtO)_2CHCH_2CH_2$	Me	546
1-27		Me	564
1-28		Me	571
1-29		Me	555
1-30	$(CH_3)_2CHOCH_2CH_2CH_2$	Me	516
1-31		Me	527
1-32		Me	513
1-33		Me	502
1-34	$Et_2NCH_2CH_2$	Me	487
1-35	$Me_2NCH_2CH_2CH_2$	Me	501
1-36	$Et_2NCH_2CH_2CH_2$	Me	529
1-37		Me	499
1-38	$EtOCH_2$	Me	474
1-39		Me	516
1-40		Me	550
1-41		H	513
1-42		H	496
1-43		H	529
1-44	$Me_2NCH_2CH_2CH_2$	H	487
1-45	$Et_2NCH_2CH_2CH_2$	H	515

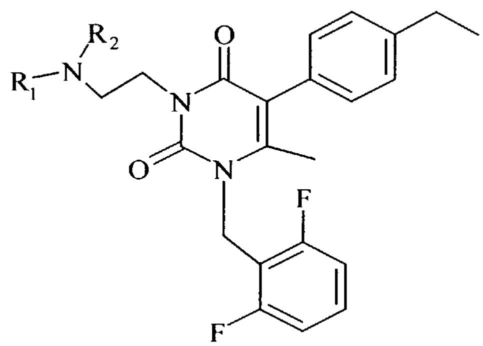
1-46		H	510
1-47		H	541
1-48	$Me_2CHCH_2OCH_2CH_2CH_2$	H	516
1-49		H	502
1-50		H	471
1-51		H	471
1-52		H	536
1-53		H	516
1-54	$PyCH_2CH_2$	$HOCH_2CH_2$	551
1-55		Me	527
1-56		Me	510
1-57		Me	543
1-58	$Me_2CHN(Me)CH_2CH_2CH_2$	Me	529
1-59		Me	524
1-60		Me	555
1-61	$Me_2CHCH_2OCH_2CH_2CH_2$	Me	530
1-62	$BuOCH_2CH_2CH_2$	Me	530
1-63		Me	499
1-64		Me	499
1-65		Me	550
1-66		Me	530
1-67	$PhCH_2CH_2CH_2$	H	506
1-68		Me	535

EXAMPLES 3

Further Representative Compounds

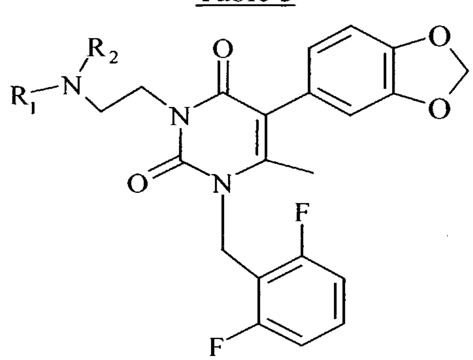
By reversing Step 1E and Step 1F in Example 1, where the boronic acid coupling is performed followed by the reductive amination, the compounds of the following Tables 2-7 were also prepared.

Table 2



Cpd. No.	R_1	R_2	MS $(MH)^+$
2-1	2-$PyCH_2CH_2$	Me	519
2-2	Bz	Me	504
2-3	2-$PyCH_2$	H	491
2-4	2-$PyCH_2CH_2$	H	505
2-5	$PhCH_2CH_2$	Me	518

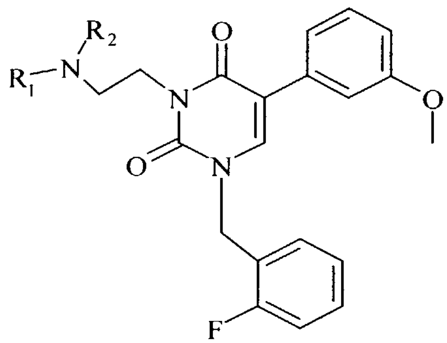
Table 3



Cpd. No.	R_1	R_2	MS $(MH)^+$
3-1	2-$PyCH_2CH_2$	Me	535

3-2	$PhCH_2CH_2$	Me	534
3-3	4-$PyCH_2CH_2$	Me	535
3-4	2-$PyCH_2CH_2$	Et	549

Table 4



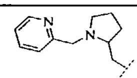
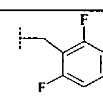
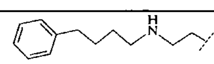
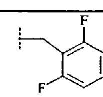
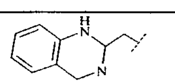
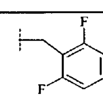
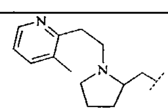
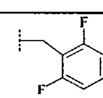
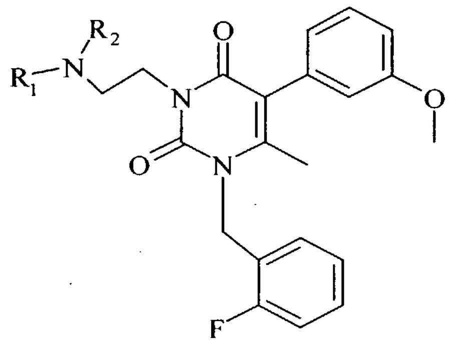
Cpd. No.	R_1	R_2	MS $(MH)^+$
4-1	$PhCH_2$	Me	474
4-2	2-$PyCH_2CH_2$	Me	489
4-3			518
4-4			520
4-5			491
4-6			547

Table 5



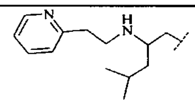
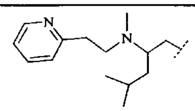
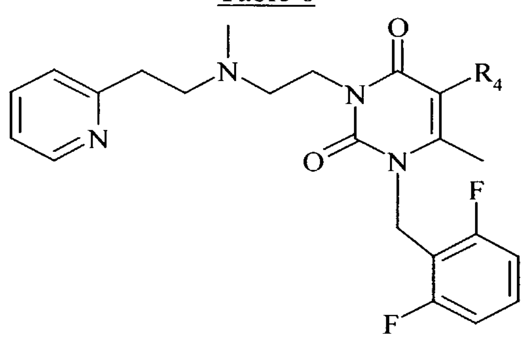
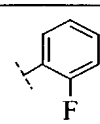
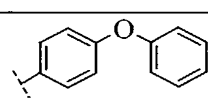
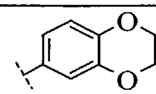
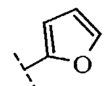
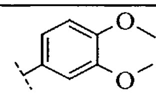
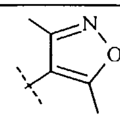
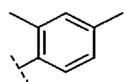
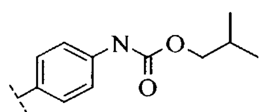
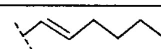
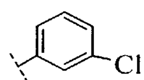
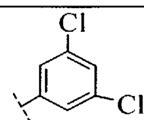
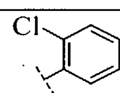
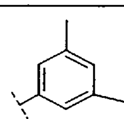
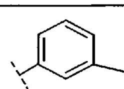
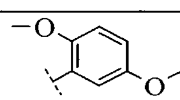
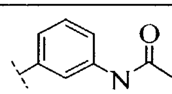
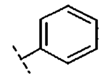
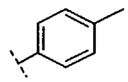
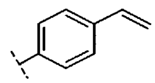
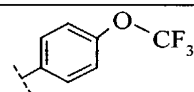
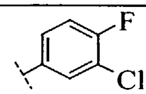
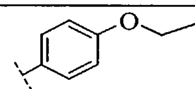
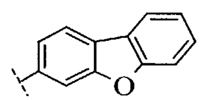
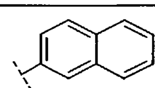
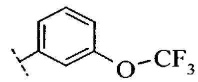
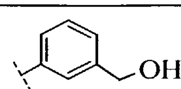
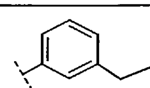
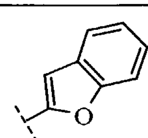
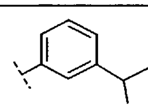
Cpd. No.	R_1	R_2	MS $(MH)^+$
5-1	$PhCH_2CH_2$	Me	488
5-2	2-$PyCH_2CH_2$	Me	503
5-3			545
5-4			559

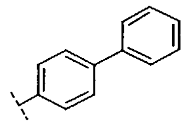
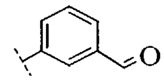
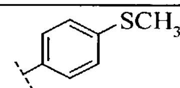
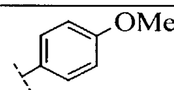
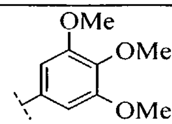
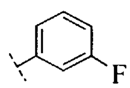
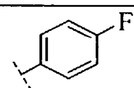
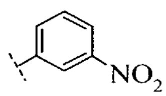
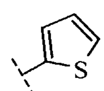
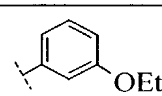
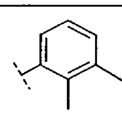
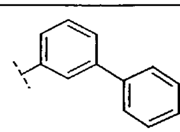
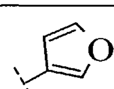
Table 6

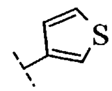
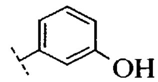
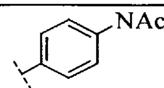
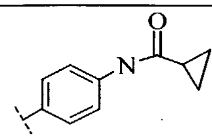
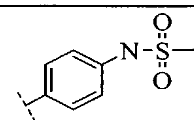
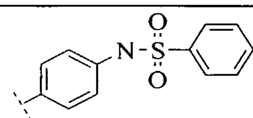
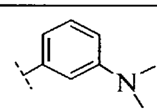
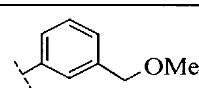
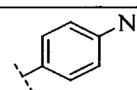
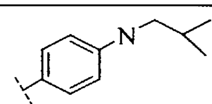
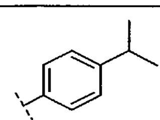
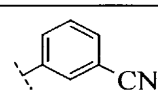
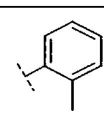


Cpd. No.	R_4	MS $(MH)^+$
6-1		509
6-2		583

6-3		549
6-4		481
6-5		551
6-6		495
6-7		519
6-8		606
6-9		497
6-10		525
6-11		559/561
6-12		525
6-13		519
6-14		505
6-15		551
6-16		548

6-17		490
6-18		504
6-19		516
6-20		575
6-21		543
6-22		535
6-23		581
6-24		541
6-25		575
6-26		521
6-27		519
6-28		531
6-29		533

6-30		567
6-31		519
6-32		537
6-33		521
6-34		581
6-35		509
6-36		509
6-37		536
6-38		497
6-39		535
6-40		519
6-41		567
6-42		481

6-43		497
6-44		507
6-45		548
6-46		573
6-47		584
6-48		645
6-49		534
6-50		535
6-51		506
6-52		562
6-53		533
6-54		516
6-55		505

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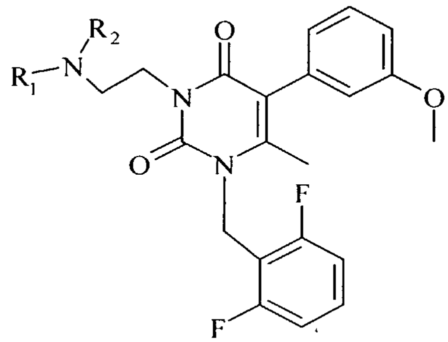

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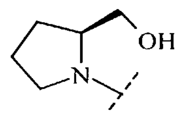
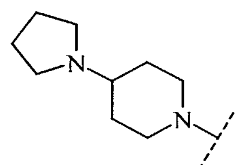
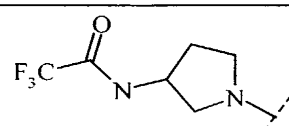
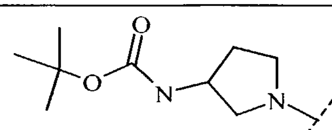
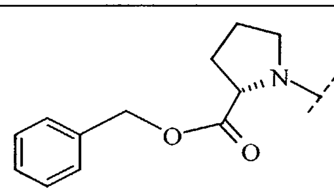
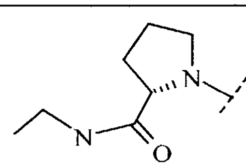
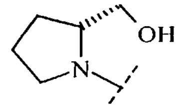
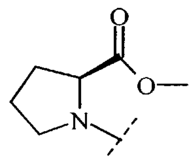
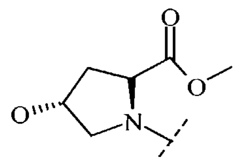
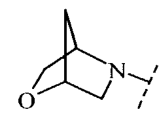
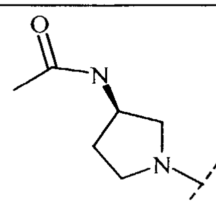
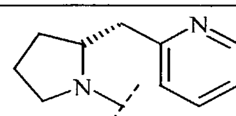
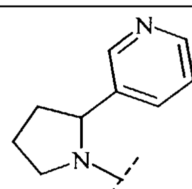
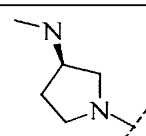
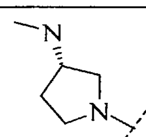
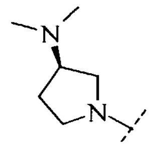
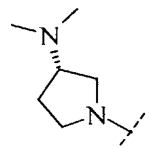
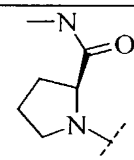
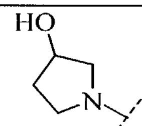
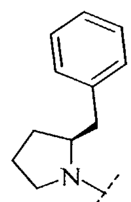
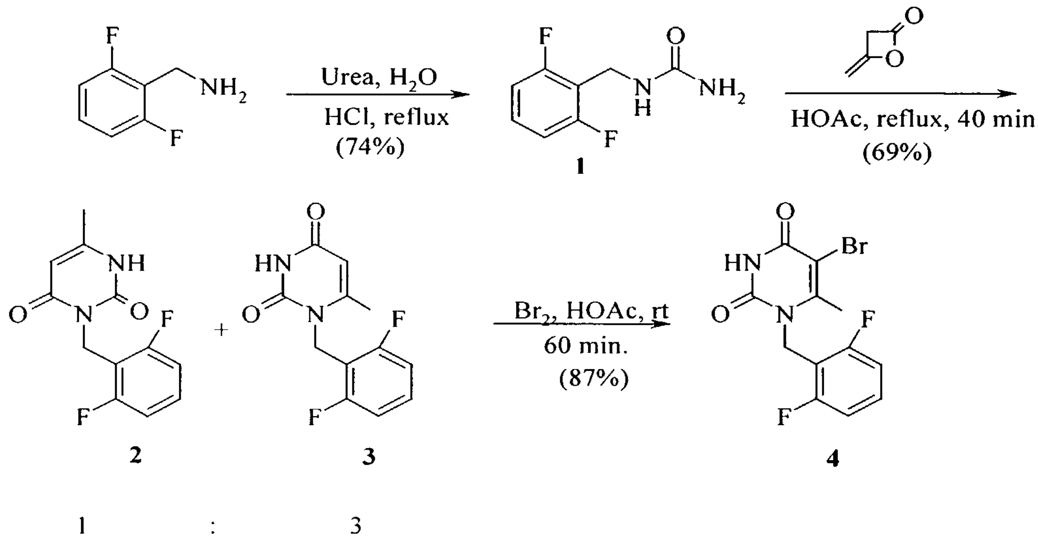
7-1		486
7-2		539
7-3		567
7-4		571
7-5		590
7-6		527

7-7		486
7-8		514
7-9		530
7-10		484
7-11		513
7-12		546
7-13		553
7-14		485
7-15		485

7-16		499
7-17		499
7-18		513
7-19		472
7-20		546

EXAMPLE 4

SYNTHESIS OF 5-BROMO-1-(2,6-DIFLUOROBENZYL)-6-METHYL-URACIL



Step A 2,6-Difluorobenzyl urea

2,6-Difluorobenzylamine (25.0 g, 0.175 mol) was added dropwise to a stirring solution of urea (41.92 g, 0.699 mol) in water (70 mL) and concentrated HCl (20.3 mL). The resulting mixture was refluxed for 2.5 hours, after which time it was cooled to room temperature. The solids that formed were filtered under vacuum, and were washed thoroughly with water. After drying under vacuum, the solids were recrystallized from EtOAc to yield the product **1** as light white needles (24.0 g, 0.129 mol, 74%).

Step B 1-(2,6-Difluorobenzyl)-6-methyl-uracil

Diketene (9.33 mL, 0.121 mol) was added in one portion to a refluxing solution of 2,6-difluorobenzyl urea **1** (20.46 g, 0.110 mol) and glacial acetic acid (110 mL). After 40 minutes at reflux, the mixture was cooled to room temperature and poured onto water (600 mL). The precipitate was collected by filtration, washed with water and dried under vacuum to yield a 1:3 mixture of isomers **2** and **3**, respectively (19.07 g, 0.076 mol, 69 %). The mixture was recrystallized from acetonitrile (~ 600

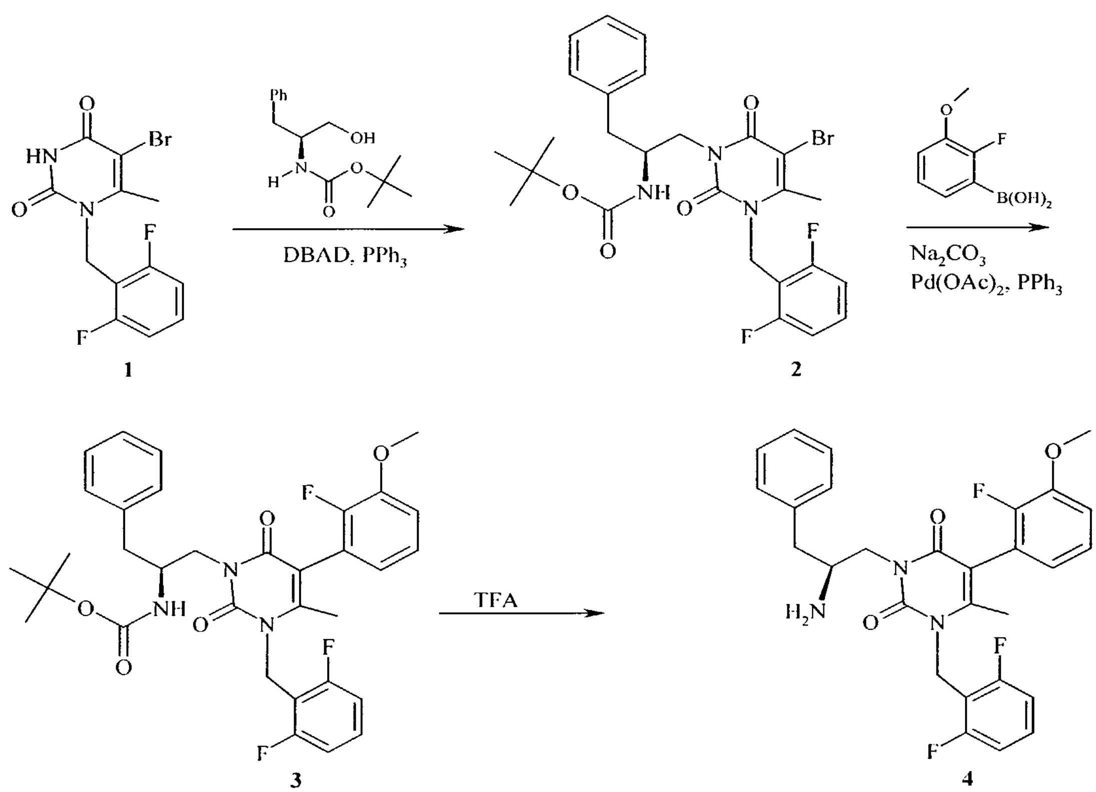
mL) to give the pure title compound **3** as white prisms (1st crop – 7.85 g, 0.031 mol, 28 %).

Step C 5-Bromo-1-(2,6-difluorobenzyl)-6-methyl-uracil

1-(2,6-Difluorobenzyl)-6-methyl-uracil **3** (7.56 g, 30 mmol) was suspended in glacial acetic acid (100 mL) and to that mixture, bromine (1.93 mL, 37.5 mmol) was added dropwise. The resulting orange solution turned into a suspension in about 5 minutes. After stirring for 1 hour at room temperature, the precipitate was filtered under vacuum and washed with water. The solids were triturated with diethyl ether and dried under vacuum to give **4** (8.6 g, 0.026 mmol, 87%).

EXAMPLE 5

FURTHER REPRESENTATIVE COMPOUNDS



Step A-1 3-(1-[2-BOC-(S)-amino-3-phenylpropyl)-5-bromo-1-(2,6-difluorobenzyl)-6-methyl-uracil

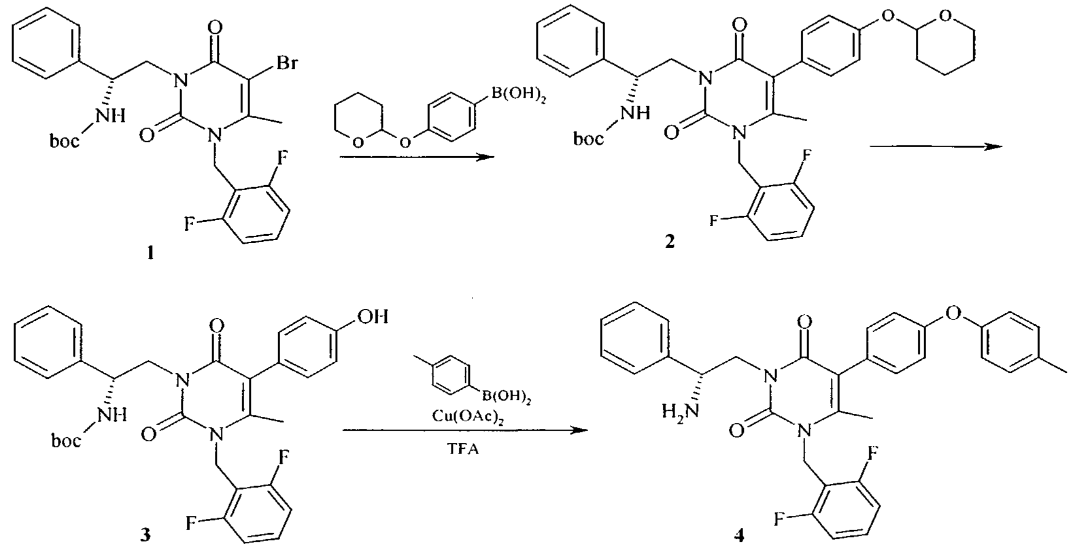
2-BOC-(S)-amino-3-phenyl-1-propanol (2.51 g, 10 mmol) and triphenylphosphine (3.14 g, 12 mmol) were added to a solution of 5-bromo-1-(2,6-difluorobenzyl)-6-methyl-uracil **1** (3.31 g, 10 mmol) in THF (50 mL). Di-*tert*-butyl azodicarboxylate (2.76 g, 12 mmol) was added in several portions over 5 minutes. After 5 minutes the reaction mixture was clear. After 1 hour the reaction mixture was concentrated and the residue was purified by silica cartridge column (hexane/EtOAc as elutant). Concentration of like fractions gave 6.8 g of an oily material which was precipitated from hexane to yield product **2** (4.95 g, 88%).

Step B-1 3-(1-[2-BOC-(S)-amino-3-phenylpropyl)-1-(2,6-difluorobenzyl)-5-(2-fluoro-3-methoxyphenyl)-6-methyl-uracil

Compound **2** (4.95 g, 8.78 mmol) and sodium carbonate (2.12g, 20 mmol) were suspended in toluene (50 mL) and dimethoxyethane (10 mL). Water (20 mL) was added and N_2 was bubbled through the reaction mixture. After 5 minutes, both layers were clear and $Pd(OAc)_2$ (394 mg, 0.2 eq) and triphenylphosphine ((921 mg, 0.4 eq) were added. The boronic acid (1.7 g, 10 mmol) was added and the reaction vessel was sealed and heated overnight at 100°C. The organic layer was separated, evaporated and purified by silica chromatography. Product containing fractions were combined and evaporated to give **3** as a brown oil (1.5 g, 28% yield).

Step C-1 3-(1-[2-(S)-Amino-3-phenylpropyl)-1-(2,6-difluorobenzyl)-5-(2-fluoro-3-methoxyphenyl)-6-methyl-uracil

Compound **3** (1.5 g, 2.5 mmol) in trifluoroacetic acid/dichloromethane (1:1, 50 mL) was heated for 4 hours. Evaporation gave a red oil which was purified by reverse phase prep HPLC using water/CH_3CN with 0.05% trifluoroacetic acid as elutant. The product containing fractions were concentrated and lyophilized to give product **4** (0.56 g, 44%, MH^+ = 510).



Step A-2 1-(2,6-Difluorobenzyl-3-[(2R)-tert-butoxycarbonylamino-2-phenyl]ethyl-6-methyl-5-(4-[tetrahydropyran-2-yloxy]phenyl)uracil

1-(2,6-Difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-6-methyl-5-bromouracil **1** (2.58 g, 4.7 mmol), tetrakis(triphenylphosphine) palladium (0) (550 mg, 0.47 mmmol), 4-hydroxyphenyl boronic acid tetrahydropyran ether (1.25 g, 5.7 mmol) and barium hydroxide (38 mL of 0.14M solution, 5.2 mmol) in a benzene/ethanol/dimethoxyethane solution (10/1/11, 90 mL) was heated at 90°C in a pressure vessel under N_2 atmosphere overnight. The organic layer was concentrated *in vacuo* and the residue was purified by silica gel chromatography (hexanes/ethyl acetate as elutant) to give 3.0 g of **2** as an off white foam.

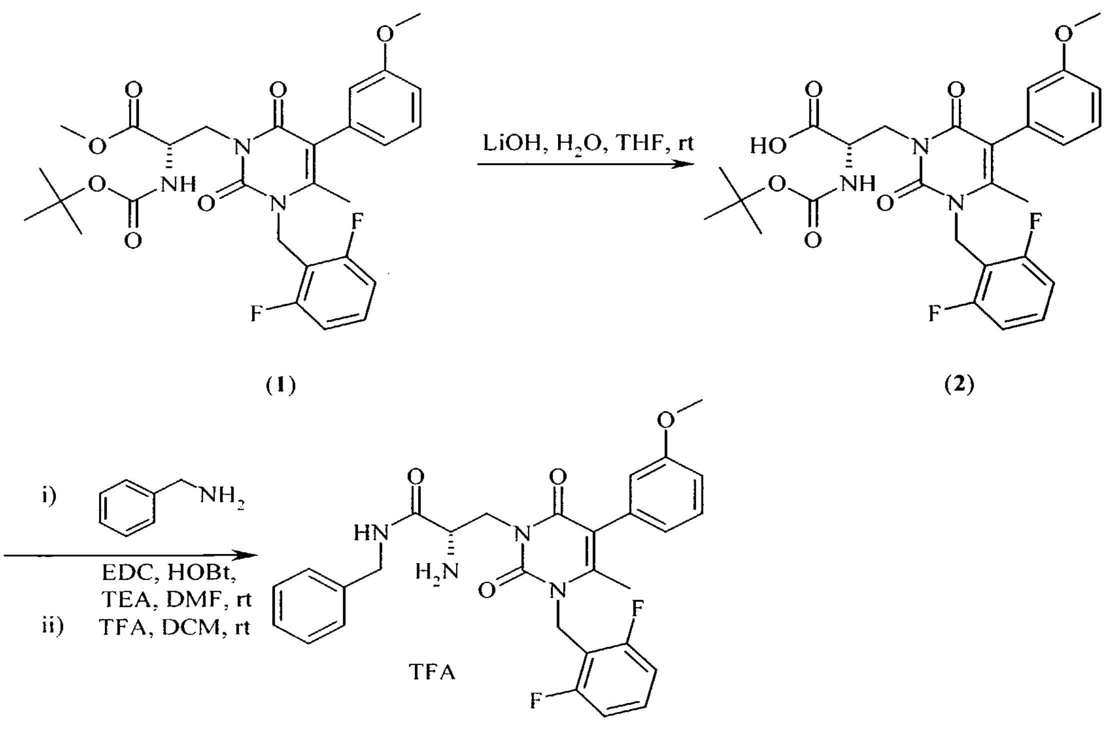
Step B-2 1-(2,6-Difluorobenzyl-3-[(2R)-tert-butoxycarbonylamino-2-phenyl]ethyl-6-methyl-5-(4-hydroxyphenyl)uracil

A mixture of **2** (3.0 g, 4.6 mmol) and pyridinium-p-toluenesulfonate (231 mg, 0.92 mmol) in ethanol (92 mL) was stirred at 45°C for 5 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in methylene chloride and H_2O. The organic layer was concentrated and the residue purified by silica gel

chromatography using hexanes/ethyl acetate as elutant to give 2.1 g of compound **3** as a yellow foam.

Step C-2 <u>1-(2,6-Difluorobenzyl-3-[(2R)-amino-2-phenyl]ethyl-5-(4-[4-tolyloxy]phenyl)uracil</u>

Substituted uracil **3** (50 mg, 0.089 mmol), p-tolylboronic acid (18 mg, 0.133 mmol), copper (II) acetate (16 mg, 0.089 mmol) and triethylamine (0.06 mL, 0.445 mmol) in CH_2Cl_2 (1 mL) were stirred for 3 days at room temperature. The reaction mixture was purified by silica gel chromatography using 1% MeOH in CH_2Cl_2 to give 30 mg of protected product. This material was dissolved in CH_2Cl_2 (1 mL) with 5 drops of trifluoroacetic acid. Purification by reverse phase HPLC/MS gave 5.0 mg of product **4** *m/z* (CI) 554 (MH^+)..



(1) (2)

(2)

Step A-3 <u>(*S*)-3-(1-*N*-*tert*-Butoxycarbonylamino-1-carboxylic acid ethyl)-1-(2,6-difluorobenzyl)-5-(3-methoxyphenyl)-6-methyluracil</u>

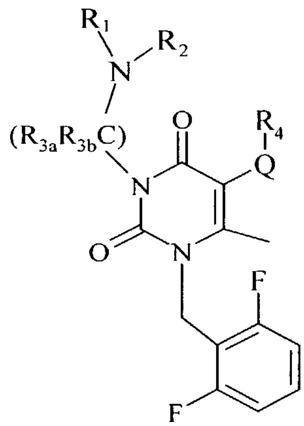
To a stirred solution of **1** (306 mg, 0.55 mmol) in tetrahydrofuran (15 mL) at room temperature, was added aqueous lithium hydroxide solution (15 mL of a 1 M solution, 15 mmol). After 2 h, most of the tetrahydrofuran was removed *in vacuo* and the resulting solution was acidified to pH 4 (with 10% aqueous citric acid solution). The resultant precipitate was extracted into ethyl acetate (2 × 15 mL) and the combined organic layer was washed with water, brine and dried ($MgSO_4$). The solvent was removed *in vacuo* to give **2** (283 mg, 94%) as a yellow oil which was not purified further, d_H (300 MHz; $CDCl_3$) 7.26-7.34 (2 H, m, Ar), 6.73-6.95 (5 H, m, Ar), 5.74 (1 H, brd, *J* 6, NH), 5.37 (1 H, d, *J* 16, CH*H*Ar), 5.22 (1 H, d, *J* 16, CH*H*Ar), 4.62 (1 H, brs, CHN), 4.32-4.49 (2 H, m, CH_2N), 3.80 (3 H, s, OCH_3), 2.17 (3 H, s, CH_3) and 1.42 (9 H, s, 3 × CH_3), *m/z* (CI) 446 (MH^+–Boc, 100%).

Step B-3 <u>(*S*)-3-(1-Amino-1-*NH*-benzylcarboxamide ethyl)-1-(2,6-difluorobenzyl)-5-(3-methoxyphenyl)-6-methyluracil trifluoroacetic acid salt</u>

To a stirred solution of **2** (20 mg, 0.037 mmol), benzylamine (15 μL, 0.14 mmol), 1-(hydroxy)benzotriazole hydrate (9 mg, 0.066 mmol) and triethylamine (10 μL, 0.074 mmol) in anhydrous *N*, *N*-dimethylformamide (1 mL) at room temperature, was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (11 mg, 0.056 mmol). After 10 h, the reaction mixture was poured into water (*ca.* 5 mL) and the resulting precipitate was extracted into ethyl acetate (*ca.* 5 mL). The organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a yellow oil, which was redissolved in a mixture of dichloromethane (1 mL) and trifluoroacetic acid (0.5 mL, 6.5 mmol) and stirred at room temperature. After 1 h, the solvent was removed *in vacuo* to give a yellow oil, which was purified by reverse phase HPLC/MS to give **3** (6 mg, 30%) as a colorless solid, *m/z* (CI) 535.2 (MH^+, 100%).

By the above procedure, the compounds of the following Table 8 were also prepared.

Table 8



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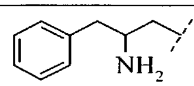
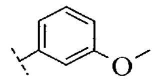
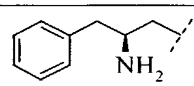
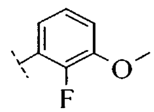
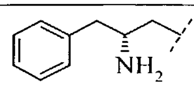
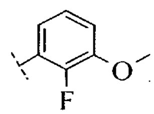
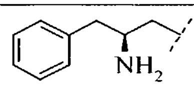
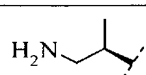
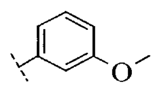
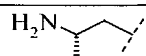
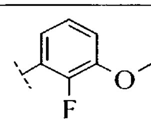
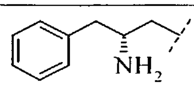
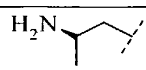
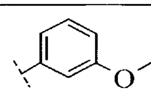
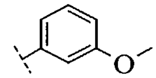
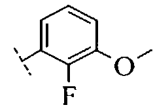
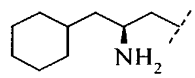
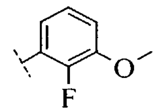
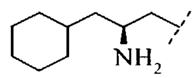
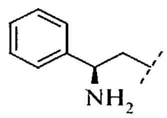
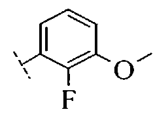
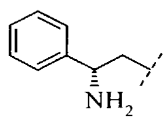
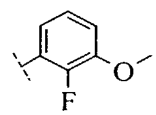
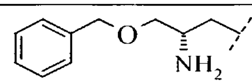
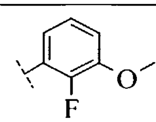
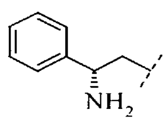
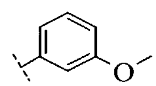
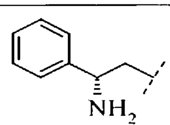
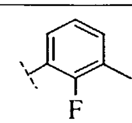
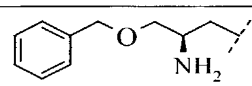
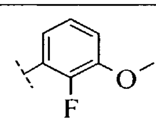
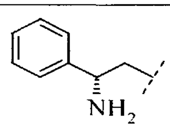
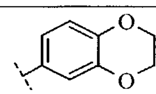
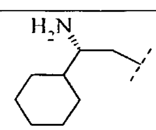
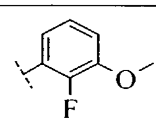
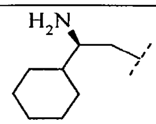
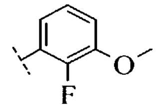
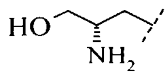
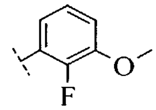
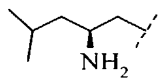
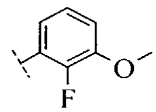
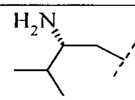
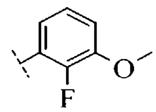
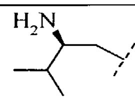
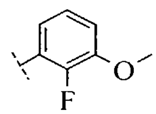
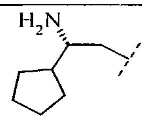
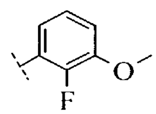
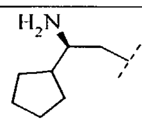
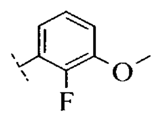
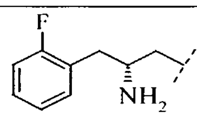
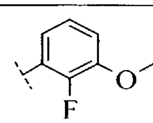
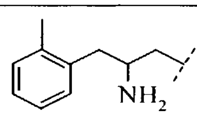
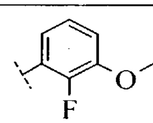
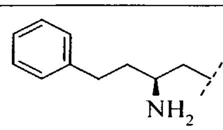
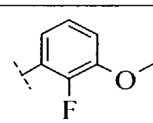
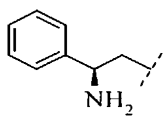
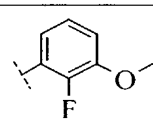
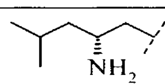
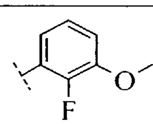
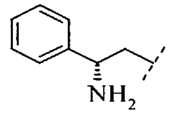
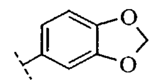
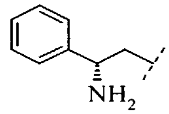
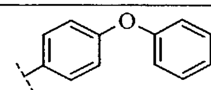
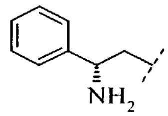
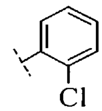
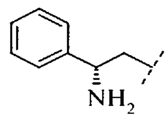
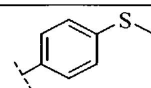
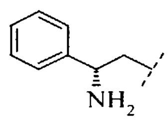
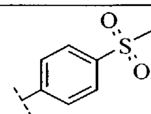
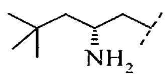
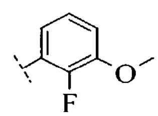
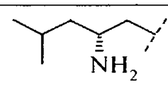
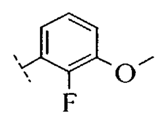
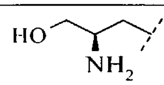
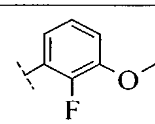
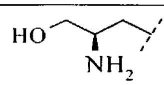
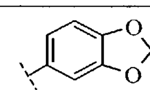
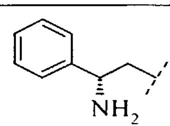
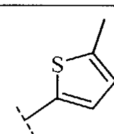
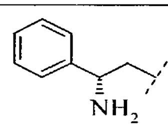
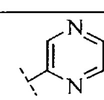
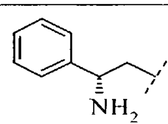
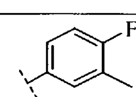
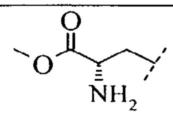
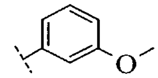
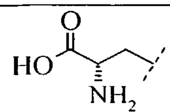
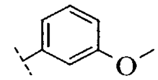
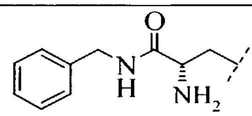
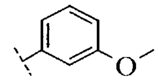
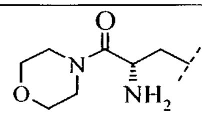
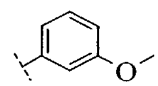
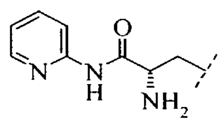
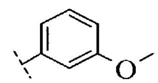
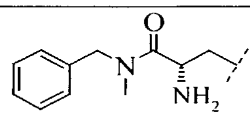
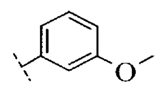
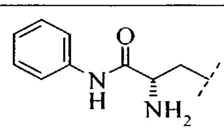
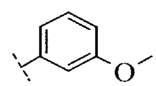
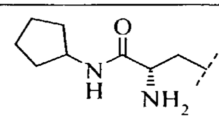
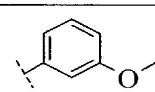
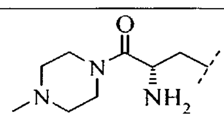
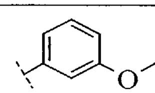
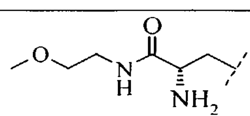
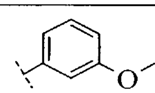
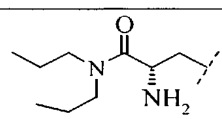
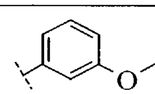
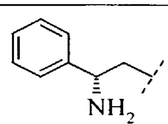
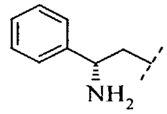
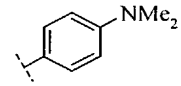
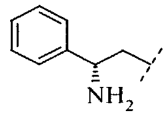
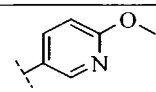
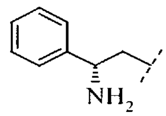
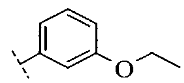
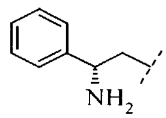
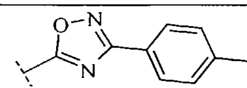
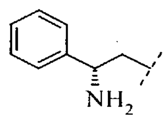
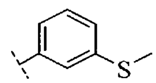
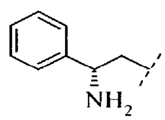
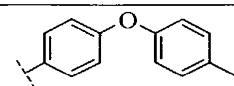
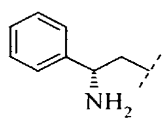
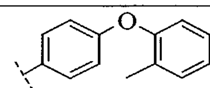
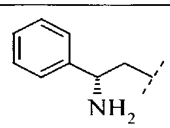
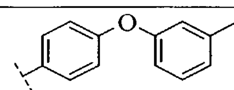
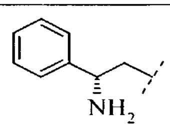
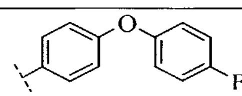
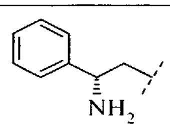
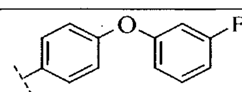
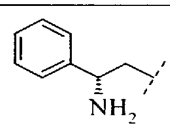
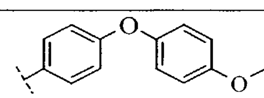
8-1			491.5	492
8-2			509.5	510
8-3			509.5	510
8-4		H	385.4	386
8-5			415.4	416
8-6			433.4	434
8-7		H	385.4	386
8-8			415.4	416

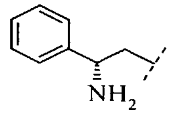
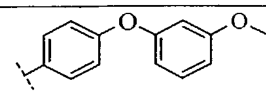
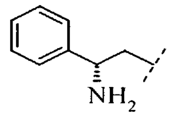
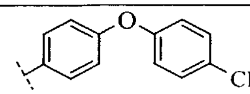
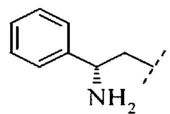
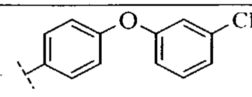
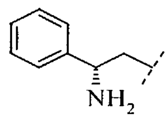
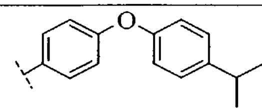
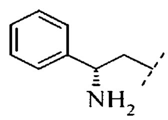
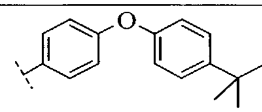
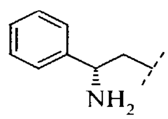
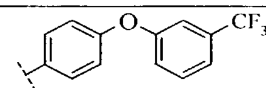
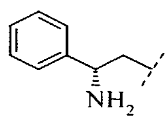
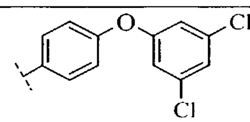
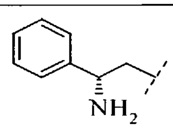
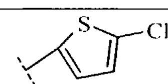
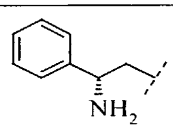
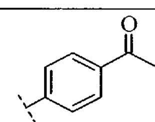
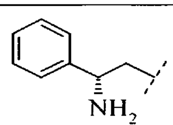
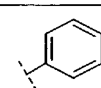
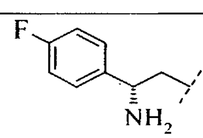
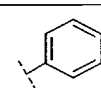
8-9			415.4	416
8-10			433.4	434
8-11			515.6	516
8-12		H	391.5	392
8-13			495.5	496
8-14			495.5	496
8-15			539.6	540
8-16			477.5	478
8-17			479.5	480
8-18			539.6	540
8-19			505.5	506
8-20			501.5	502.2

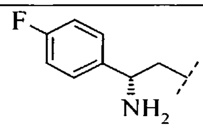
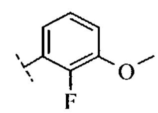
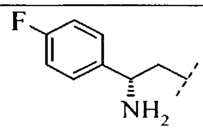
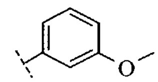
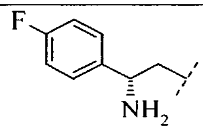
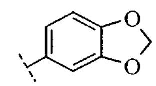
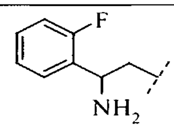
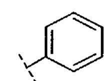
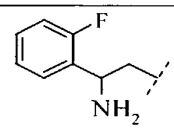
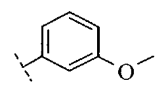
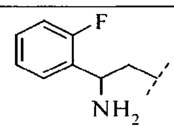
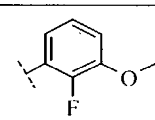
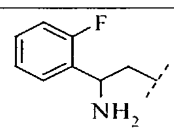
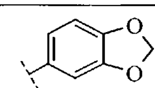
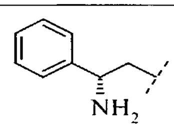
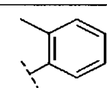
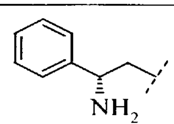
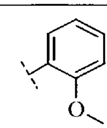
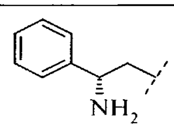
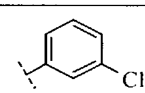
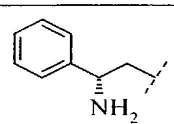
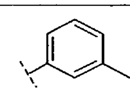
8-21			501.5	502.2
8-22			465.5	450
8-23			475.5	476.2
8-24			461.5	462.2
8-25			461.5	462.2
8-26			487.5	488.2
8-27			487.5	488.2
8-28			527.5	528
8-29			523.6	524
8-30			523.6	524
8-31			495.5	496
8-32			475.5	476.2

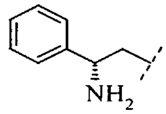
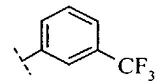
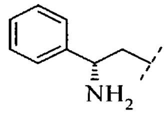
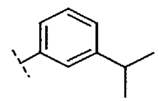
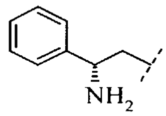
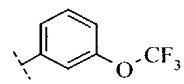
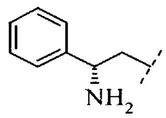
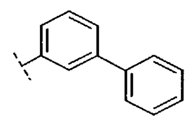
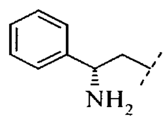
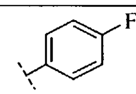
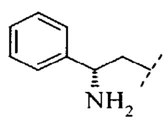
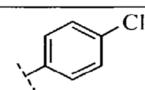
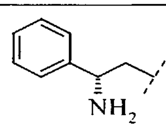
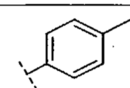
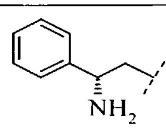
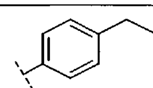
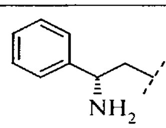
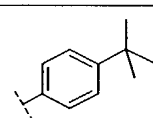
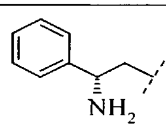
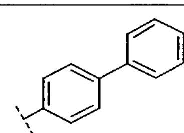
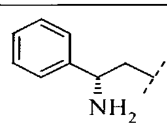
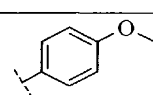
8-33			491.5	492
8-34			539.6	540
8-35			481.9	482
8-36			493.6	494
8-37			525.6	526
8-38			489.5	490.2
8-39			475.5	476.2
8-40			449.4	450
8-41			445.4	446
8-42			467.5	469
8-43			449.5	450
8-44			479.5	480

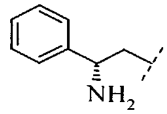
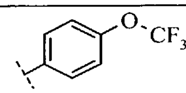
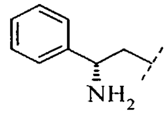
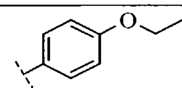
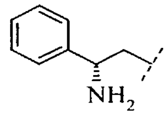
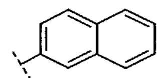
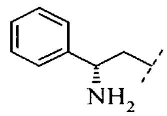
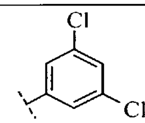
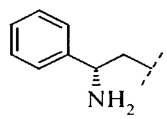
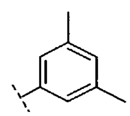
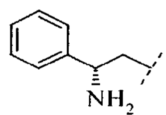
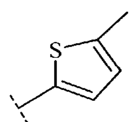
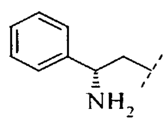
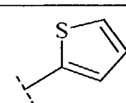
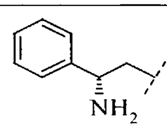
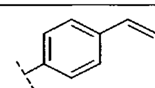
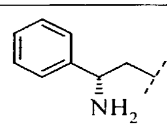
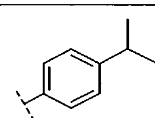
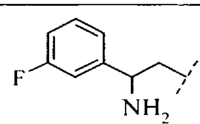
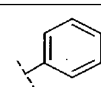
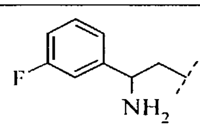
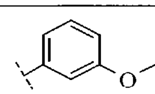
8-45			459.4	460.2
8-46			445.4	446.1
8-47			534.6	535.2
8-48			514.5	515.2
8-49			521.5	522.2
8-50			548.6	549.2
8-51			520.3	521.2
8-52			512.6	513.2
8-53			527.6	528.2
8-54			502.5	503.2
8-55			528.6	529.3
8-56		H	371.4	372.1

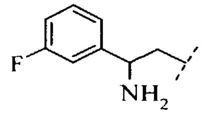
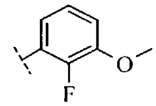
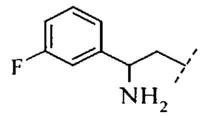
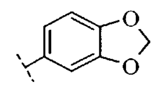
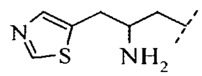
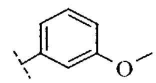
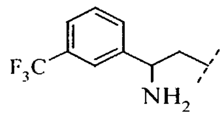
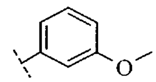
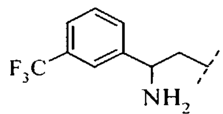
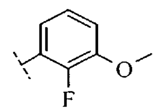
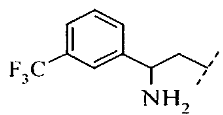
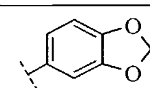
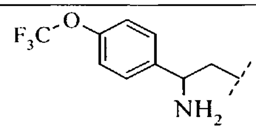
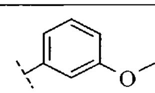
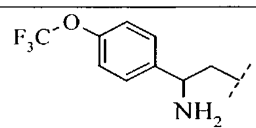
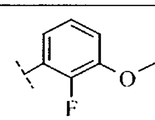
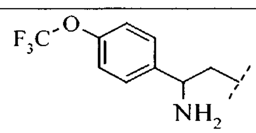
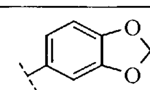
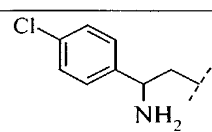
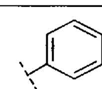
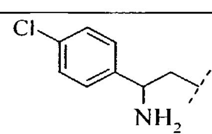
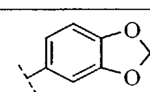
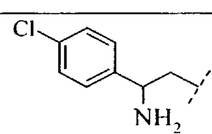
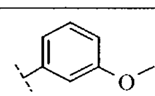
8-57			490.6	491.2
8-58			478.5	479.1
8-59			491.5	492.2
8-60			515.5	516.2
8-61			493.6	494.1
8-62			553.6	554.2
8-63			553.6	554.2
8-64			553.6	554.2
8-65			557.6	558.2
8-66			557.6	558.2
8-67			569.6	570.2

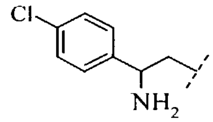
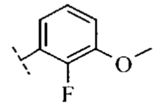
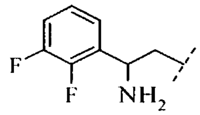
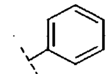
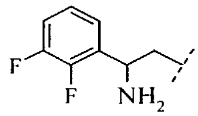
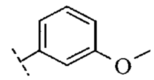
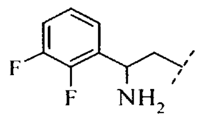
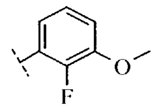
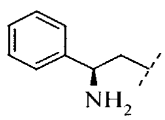
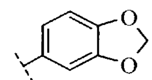
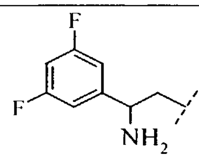
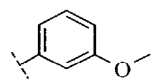
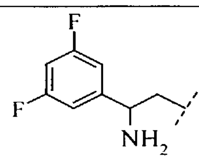
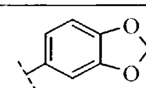
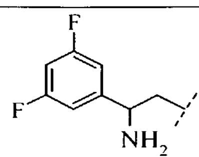
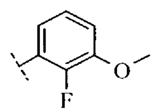
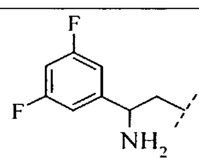
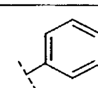
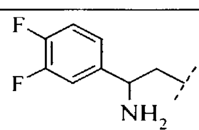
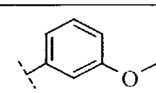
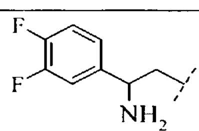
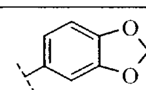
8-68			569.6	570.2
8-69			574.0	574.2
8-70			574	574.2
8-71			581.7	582.3
8-72			595.7	596.3
8-73			607.6	608.2
8-74			608.5	608.1
8-75			488	488.1
8-76			489.5	490.2
8-77			447.5	488.2
8-78			465.5	466.1

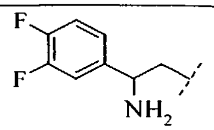
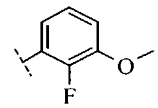
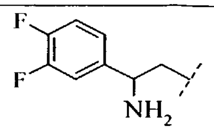
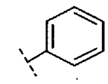
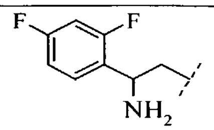
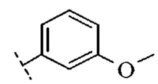
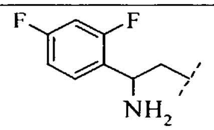
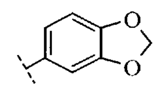
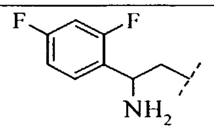
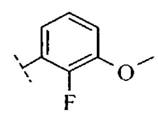
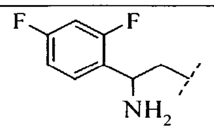
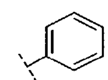
8-79			513.5	514.1
8-80			495.5	496.2
8-81			509.5	510.1
8-82			465.5	466.2
8-83			495.5	496.2
8-84			513.5	514.2
8-85			509.5	510.2
8-86			461.5	462
8-87			477.5	478
8-88			481.9	482
8-89			461.5	462

8-90			515.5	516
8-91			489.6	490
8-92			531.5	532
8-93			523.6	524
8-94			465.5	466
8-95			481.9	482
8-96			461.5	462
8-97			475.5	476
8-98			503.6	504
8-99			523.6	524
8-100			477.5	478

8-101			531.5	532
8-102			491.5	482
8-103			497.5	498
8-104			516.4	516
8-105			475.5	476
8-106			467.5	468
8-107			453.5	454
8-108			476.5	474
8-109			489.6	490
8-110			465.5	466.1
8-111			495.5	496.2

8-112			513.5	514.2
8-113			509.5	510.1
8-114			498.6	498
8-115			545.5	546.2
8-116			563.5	564.2
8-117			559.5	560.2
8-118			561.5	562.2
8-119			579.5	580.2
8-120			575.5	576.2
8-121			481.9	482.1
8-122			525.9	526.1
8-123			512	512.1

8-124			529.9	530.1
8-125			483.5	484.1
8-126			513.5	496.2
8-127			531.5	532.1
8-128			491.5	492.2
8-129			513.5	514.2
8-130			527.5	528.1
8-131			531.5	532.2
8-132			483.5	484.1
8-133			513.5	514.2
8-134			527.5	528.2

8-135			531.5	532.2
8-136			483.5	484.1
8-137			513.5	514.1
8-138			527.5	528.2
8-139			531.5	532.2
8-140			483.5	484.1

EXAMPLE 6

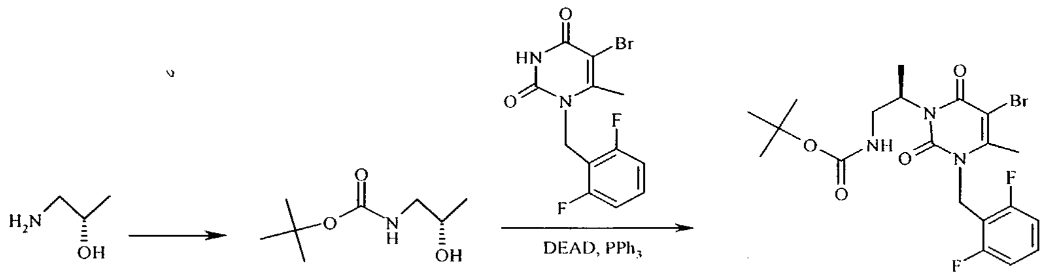
SYNTHESIS OF BORONIC ACIDS

Step A <u>2-Fluoro-3-methoxyphenylboronic acid</u>

n-Butyl lithium (20 mL, 2.5M) was added to a solution of tetramethylpiperidine (8.44 mL, 50 mmol) in THF (125 mL) at –78°C. The reaction mixture was stirred at –78°C for 1.5 hours. 2-Fluoroanisole (6.31 g, 50 mmol) was added and the mixture was stirred for 8 hours at –78°C. Trimethyl borate (6.17 mL, 55 mmol) was added and the reaction mixture was allowed to warm slowly to room temperature overnight. The mixture was poured into 1N HCl (250 mL). Extraction with EtOAc followed by evaporation gave a sticky solid which was triturated with hexanes to give product (2.19 g, 26% yield).

EXAMPLE 7

SYNTHESIS OF REPRESENTATIVE COMPOUNDS



1

2

Step A BOC-(S)-1-amino-2-propanol

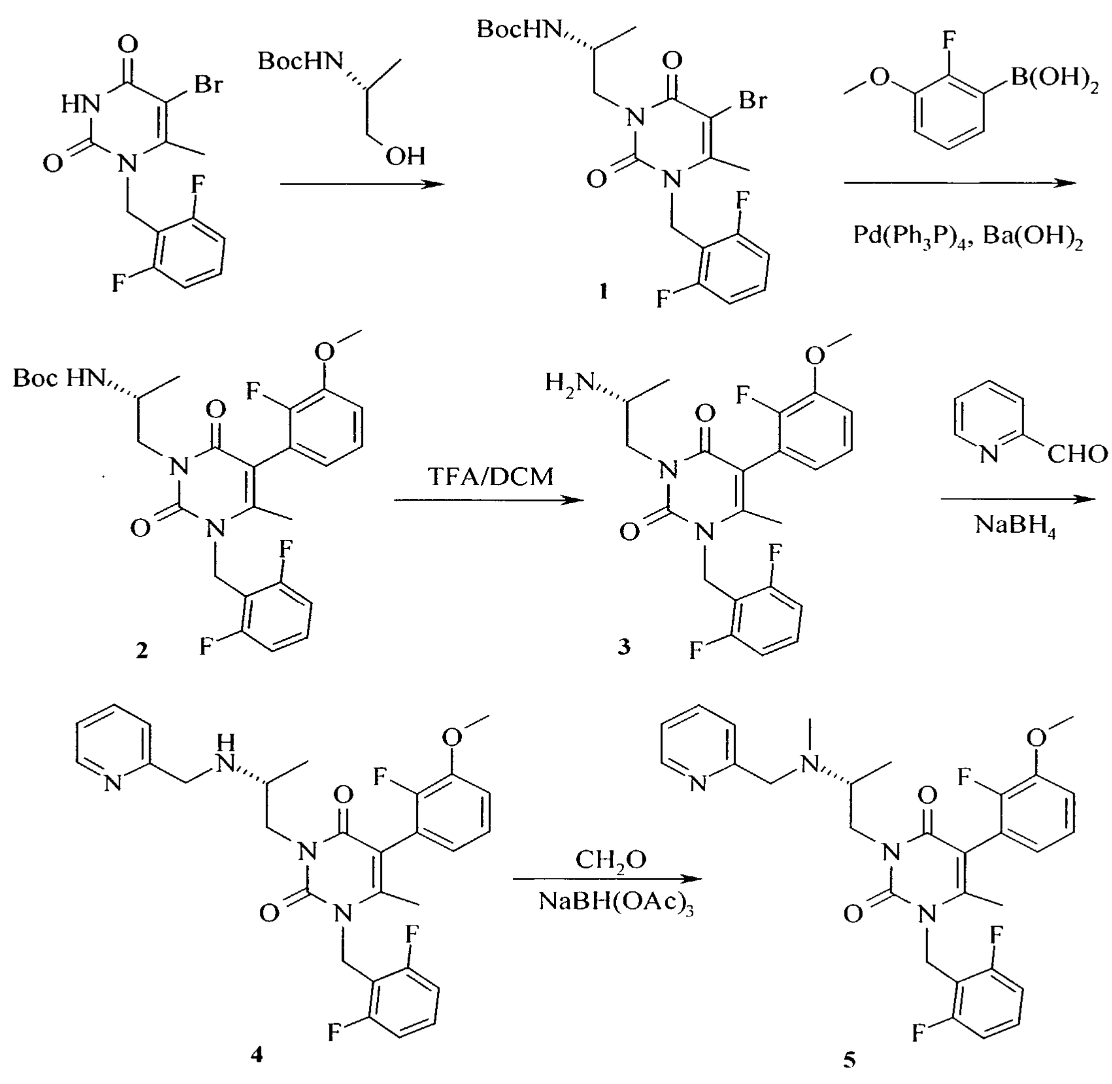
Di-t-butyl dicarbonate (6.76 g, 31 mmol) was added portionwise to a stirred solution of (S)-1-amino-2-propanol and triethylamine (4.4 mL, 31.5 mmol) in CH_2Cl_2 (75 mL) at 0°C. The reaction mixture was stirred for 1 hour at 0°C and for 30 minutes at room temperature. Evaporation gave product **1** which was used without further purification.

Step B 3-(2-BOC-(R)-1-aminopropyl)-5-bromo-1-(2,6-difluorobenzyl)-6-methyl-uracil

5-Bromo-1-(2,6-difluorobenzyl)-6-methyluracil (3.31 g, 10 mmol) was suspended in THF (200 mL). Compound **1** (1.84 g, 10.5 mmol) and triphenylphosphine (3.93 g, 15 mmol) were added and the mixture was stirred. DEAD (2.36 mL, 15 mmol) was added and the reaction mixture became a solution. After stirring overnight, the volatiles were removed and the residue was chromatographed on silica using EtOAc/hexanes as elutant to give white solid **2** (4.57 g, 94% yield).

EXAMPLE 8

SYNTHESIS OF REPRESENTATIVE COMPOUNDS



Step A

A solution of N-(t-butyloxycarbonyl)-D-α-alaninol (1.75g, 10 mmol) in anhydrous THF (15 mL) was treated with 5-bromo-1-(2,6-difluorobenzyl)-6-methyluracil (3.31 g, 10 mmol) and triphenylphosphine (3.15 g, 12 mmol) at ambient temperature, then di-*tert*-butylazodicarboxylate (2.76 g, 12 mmol) was introduced. The reaction mixture was stirred at ambient temperature for 16 hours and volatiles were

evaporated. The residue was partitioned between saturated $NaHCO_3/H_2O$ and EtOAc. The organic layer was dried (sodium sulfate), evaporated, and purified by flash chromatography (silica, 1:2 EtOAc/hexanes) to give compound **1** (4.69 g, 96.1 %), MS (CI) *m/z* 388.0, 390.0 (MH^+-Boc).

Step B

To compound **1** (1.0 g, 2.05 mmol) in benzene/EtOH/ethylene glycol dimethyl ether (20/2/22 mL) was added 2-fluoro-3-methoxyphenylboronic acid (435 mg, 2.56 mmol) and saturated $Ba(OH)_2$/water (~ 0.5 M, 15 mL). The reaction mixture was deoxygenated with N_2 for 10 min, tetrakis(triphenylphosphine) palladium (0) (242 mg, 0.21 mmol) was added and the reaction mixture was heated at 80°C overnight under the protection of N_2. The reaction mixture was partitioned between brine and EtOAc. The organic layer was dried (sodium sulfate), evaporated, purified by flash chromatography (silica, 40% EtOAc/hexanes) to give compound **2** (450 mg, 41.2%), MS (CI) *m/z* 434.2 (MH^+-Boc).

Step C

TFA (2 mL) was added to a solution of **2** (267 mg, 0.5 mmol) in dichloromethane (2 mL) and the reaction mixture was stirred at ambient temperature for 1 hour. Volatiles were evaporated and the residue was partitioned between saturated $NaHCO_3$/water and EtOAc. The organic layer was dried (sodium sulfate), evaporated, and purified by reverse phase HPLC (C-18 column, 15-75% acetonitrile/water) to give compound **3**, MS (CI) *m/z* 434.2 (MH^+).

Step D

2-Pyridinecarboxyaldehyde (80 mg, 0.75 mmol) was added to a solution of **3** (267 mg, 0.5 mmol) in MeOH (5 mL) and the reaction mixture was stirred at ambient temperature for 10 hours. $NaBH_4$ (56 mg, 1.5 mmol) was added and the reaction mixture was kept at ambient temperature for 10 minutes. Volatiles were evaporated and the residue was partitioned between saturated $NaHCO_3$/water and

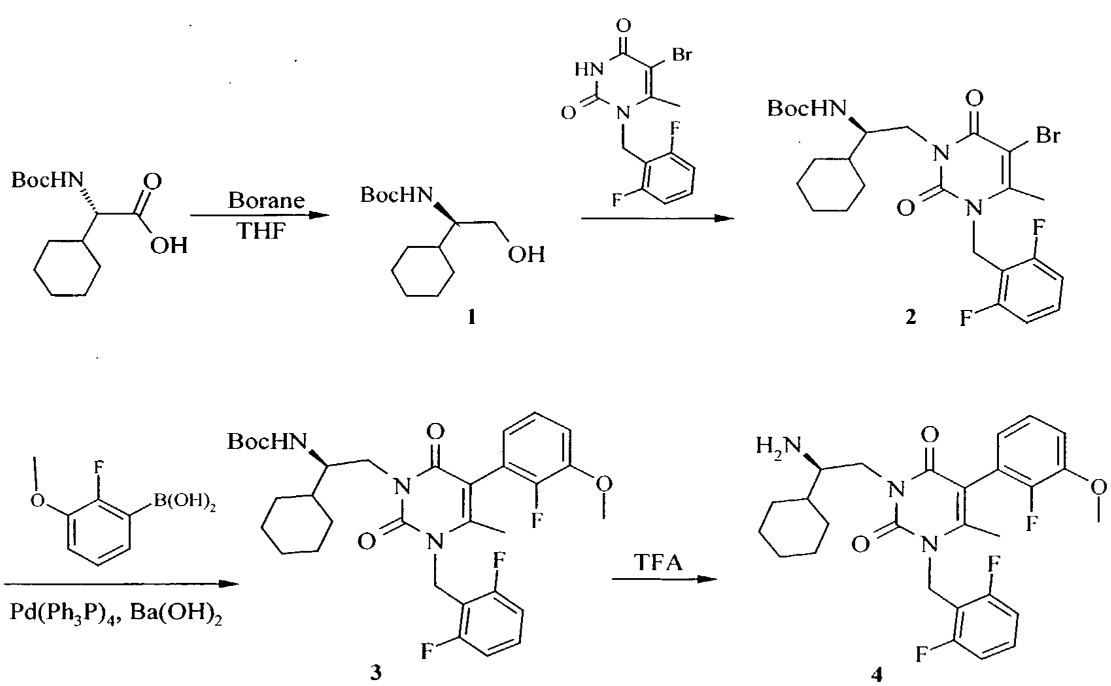
dichloromethane. The organic layer was dried (sodium sulfate), evaporated, and purified by reverse phase HPLC (C-18 column, 15-75% acetonitrile/water) to give compound **4**, MS (CI) *m/z* 525.20 (MH^+).

Step E

To a solution of **4** (20 mg, 0.04 mmol) in dichloroethane (2 mL) was added 1 drop of formaldehyde (37% solution in water) and $NaBH(OAc)_3$ (16 mg, 0.08 mmol). The reaction mixture was stirred at ambient temperature for 2 hours, volatiles were evaporated and the residue was partitioned between water and dichloromethane. The organic layer was dried (sodium sulfate), evaporated, and purified by reverse phase HPLC (C-18 column, 15-75% acetonitrile/water) to give compound **5**, MS (CI) *m/z* 539.20 (MH^+).

EXAMPLE 9

SYNTHESIS OF REPRESENTATIVE COMPOUNDS



Step A

A solution of N^{α}-(t-butyloxycarbonyl)-L-α-cyclohexylglycine (2.0 g, 7.77 mmol) in anhydrous THF (10 mL) was cooled down to 0°C. Borane solution (1 M in THF, 15.5 mL, 15.5 mmol) was added slowly and then warmed to ambient temperature, and the reaction mixture was stirred at ambient temperature for 2 h. The reaction was quenched with MeOH (5 mL), volatiles were evaporated and the residue was partitioned between water and EtOAc. The organic layer was washed with saturated $NaHCO_3$/water and brine, and then was dried (sodium sulfate) and evaporated to give compound **1** (1.26g, 66.7%), MS (CI) *m/z* 144.20 (MH^+-Boc).

Step B

A solution of **1** (638 mg, 2.62 mmol) in THF (10 mL) was treated with 5-bromo-1-(2,6-difluorobenzyl)-6-methyluracil (869 mg, 2.62 mmol) and triphenylphosphine (1.03g, 3.93 mmol) at ambient temperature, then di-*tert*-butylazodicarboxylate (906 mg, 3.93 mmol) was introduced. The reaction mixture was stirred at ambient temperature for 16 h and volatiles were evaporated. The residue was partitioned between saturated $NaHCO_3/H_2O$ and EtOAc. The organic layer was dried (sodium sulfate), evaporated, and purified by flash chromatography (silica, 25% EtOAc/hexanes) to give compound **2** (1.39 g, 95.4%), MS (CI) *m/z* 456.10, 458.10 (MH^+-Boc).

Step C

Compound **2** (1.0 g, 1.79 mmol) in benzene/EtOH/ethylene glycol dimethyl ether (20/2/22 mL) was added 2-fluoro-3-methoxyphenylboronic acid (382 mg, 2.24 mmol) and saturated $Ba(OH)_2$/water (~ 0.5 M, 15 mL). The reaction mixture was deoxygenated with N_2 for 10 min, tetrakis(triphenylphosine) palladium (0) (208 mg, 0.18 mmol) was added and the reaction mixture was heated at 80°C overnight under the protection of N_2. The reaction mixture was partitioned between brine and EtOAc. The organic layer was dried (sodium sulfate), evaporated, and purified by flash

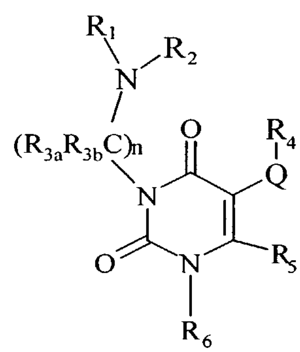
chromatography (silica, 30% EtOAc/hexanes) to give compound **3** (348 mg, 32.3%), MS (CI) *m/z* 502.20 (MH^+-Boc).

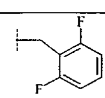
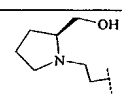
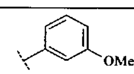
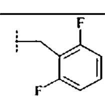
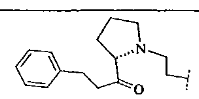
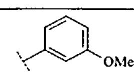
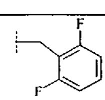
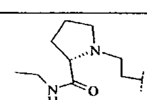
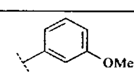
Step D

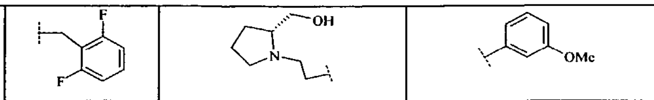
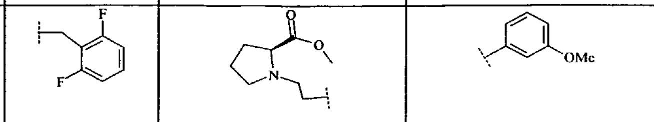
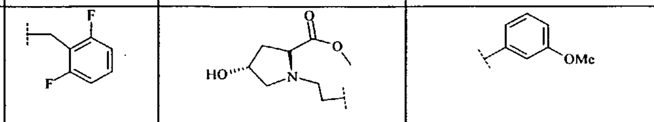
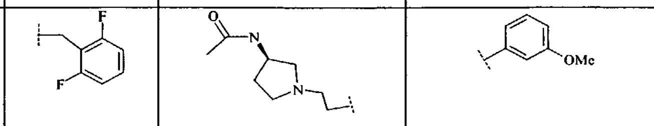
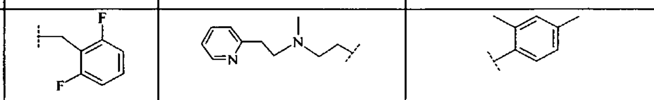
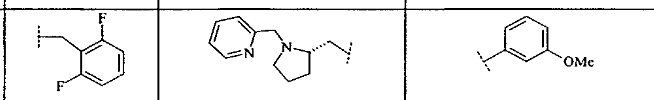
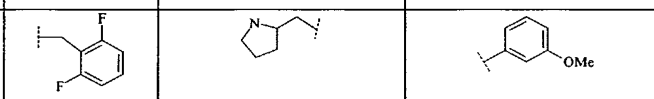
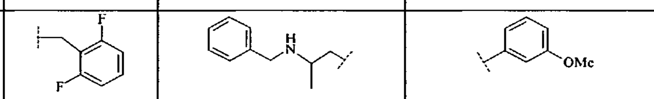
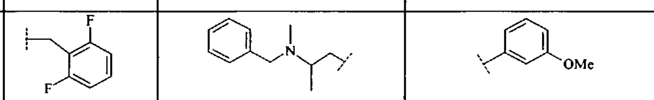
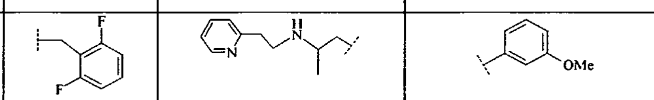
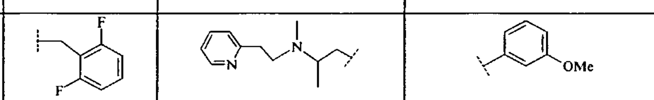
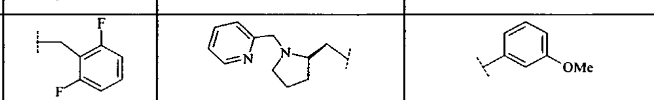
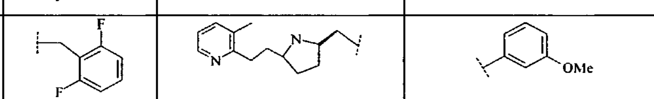
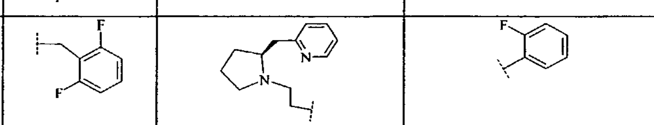
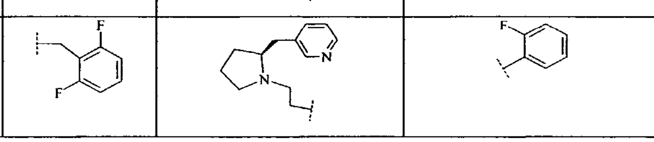
A solution of **3** (300 mg, 0.5 mmol) in dichloromethane (2 mL) was added TFA (2 mL) and the reaction mixture was stirred at ambient temperature for 1 h. Volatiles were evaporated and the residue was partitioned between saturated $NaHCO_3$/water and EtOAc. The organic layer was dried (sodium sulfate), evaporated, and purified by reverse phase HPLC (C-18 column, 15-75% ACN/water) to give compound **4**, MS (CI) *m/z* 502.20 (MH^+).

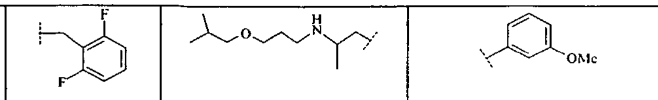
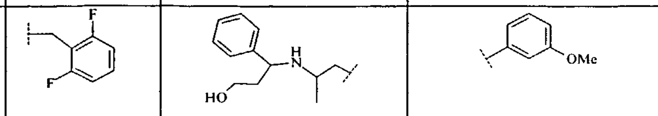
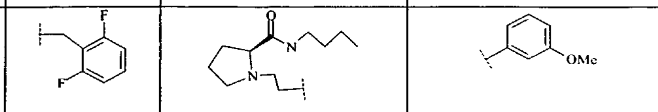
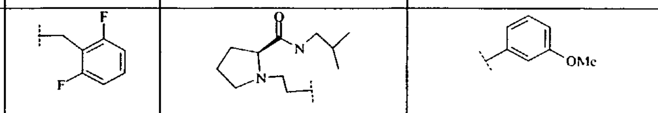
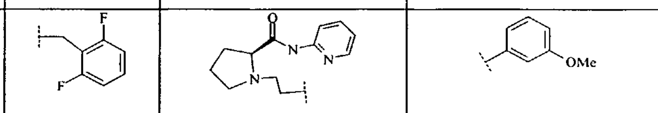
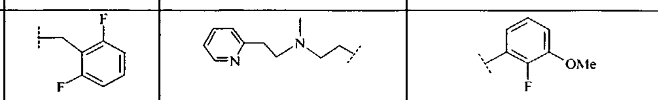
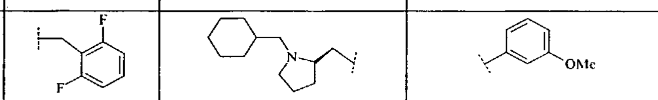
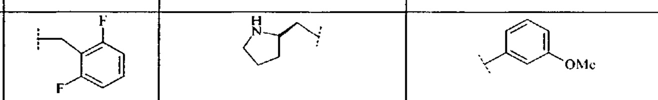
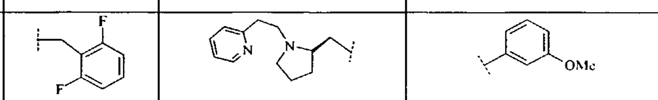
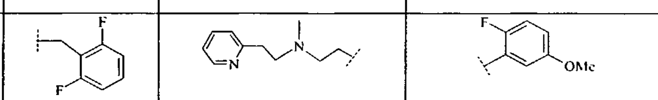
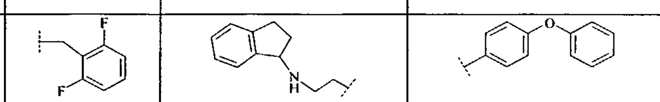
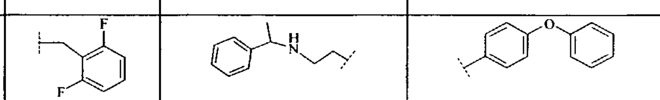
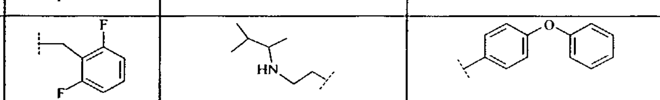
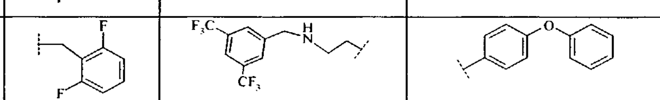
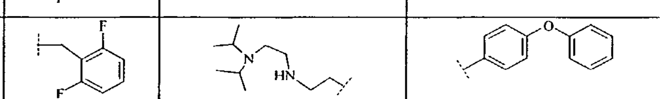
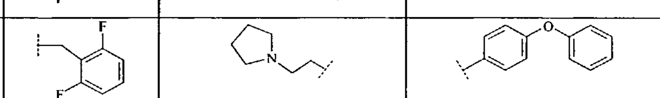
By the above procedure, the compounds of the following Table 9 were also prepared.

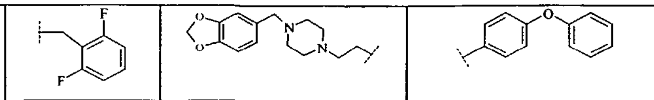
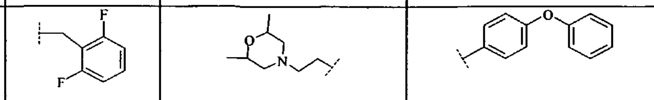
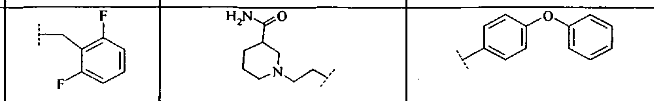
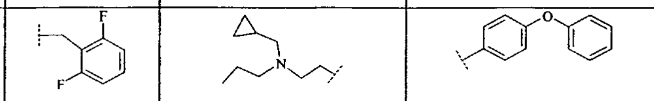
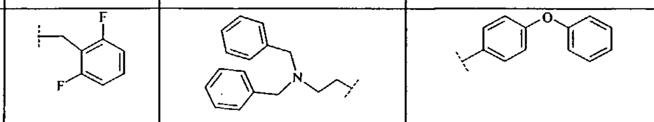
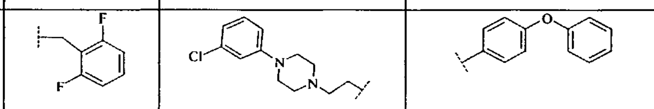
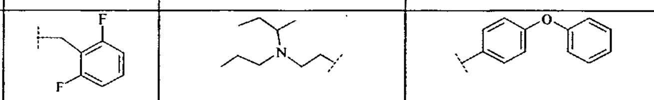
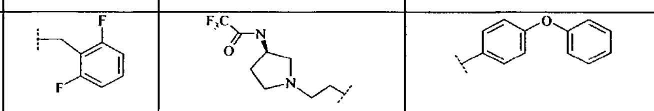
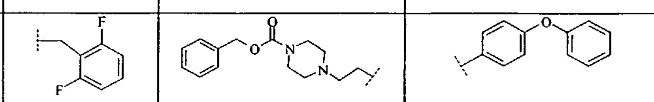
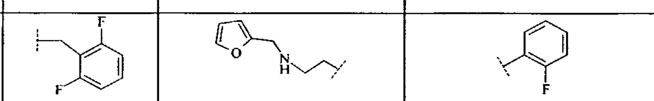
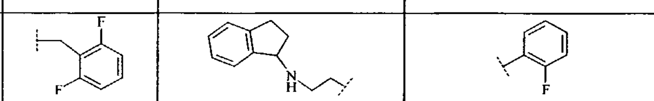
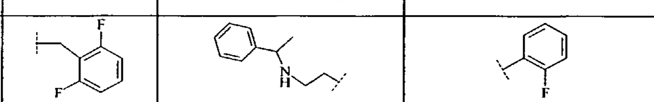
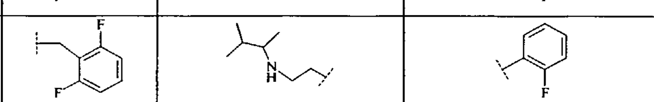
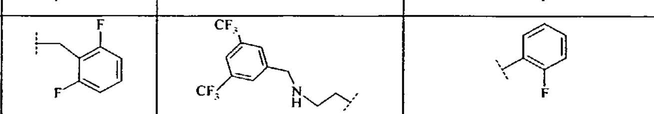
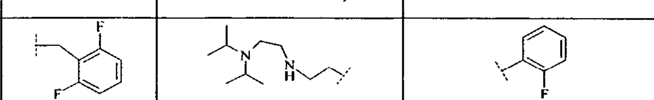
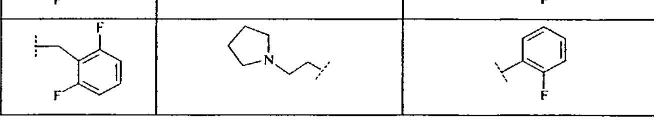
Table 9

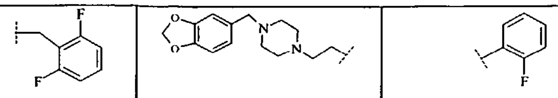
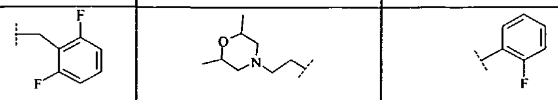
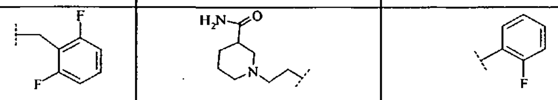
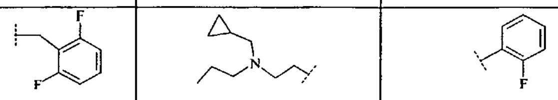
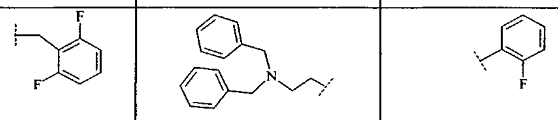
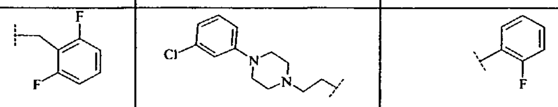
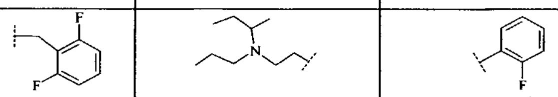
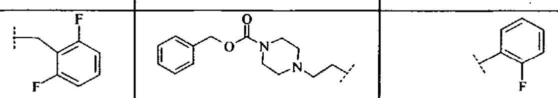
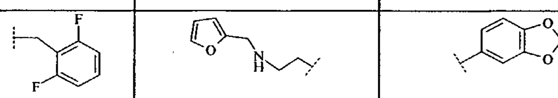
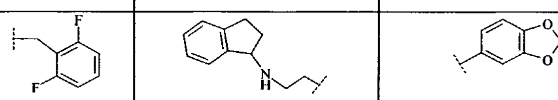
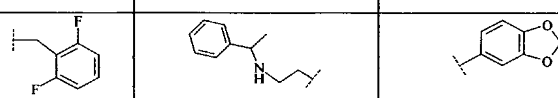
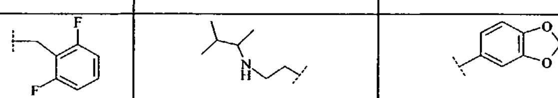
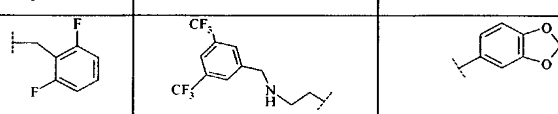
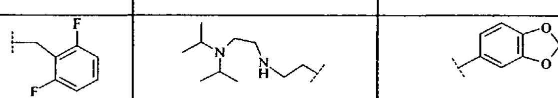
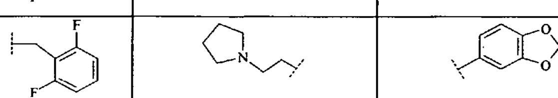
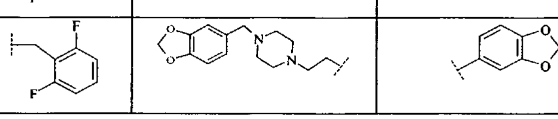


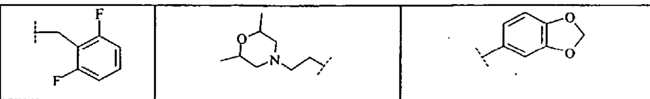
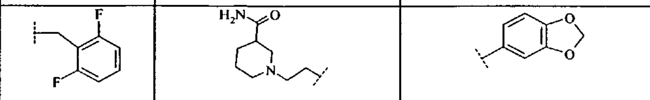
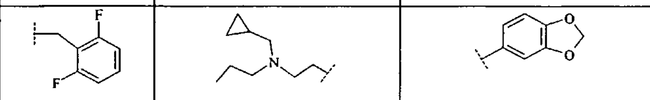
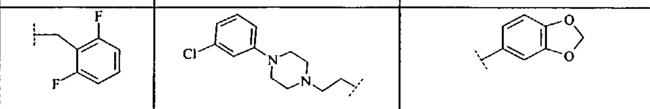
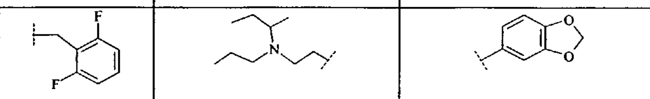
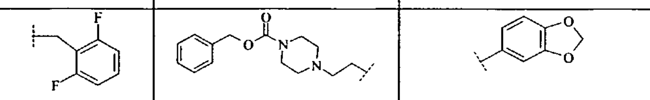
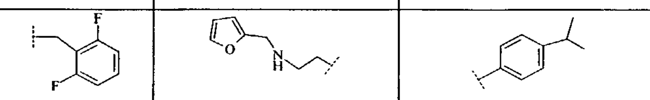
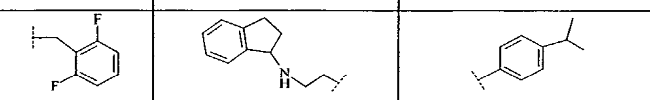
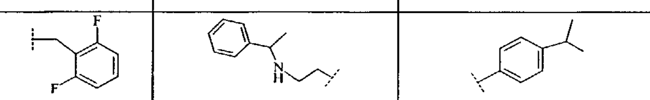
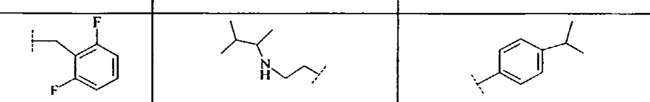
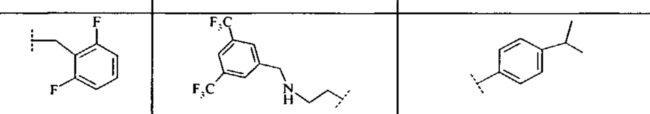
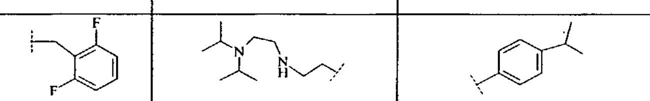
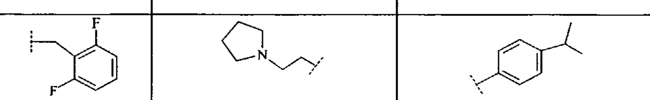
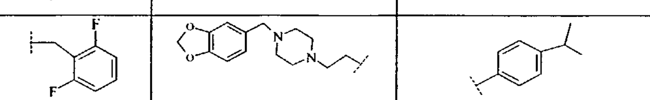
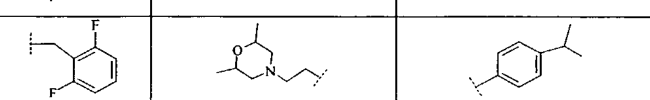
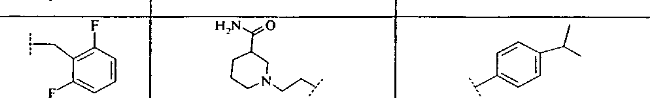
Cpd. No.	R_5	R_6	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	MW (obs.)
9-1	Me				485.5	486
9-2	Me				589.6	590
9-3	Me				526.6	527

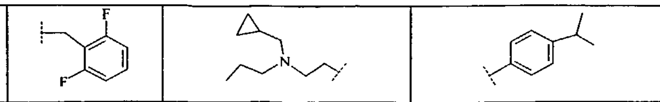
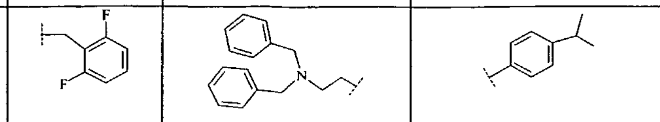
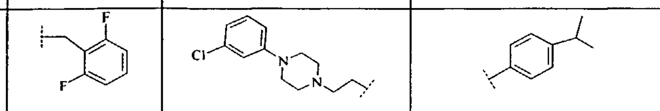
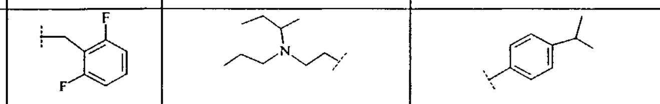
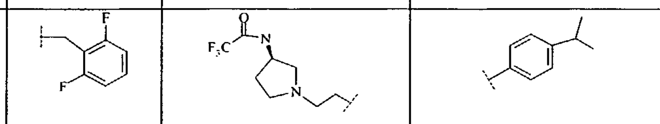
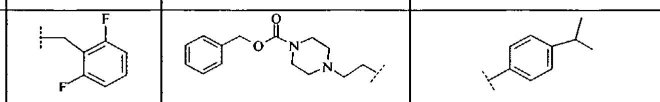
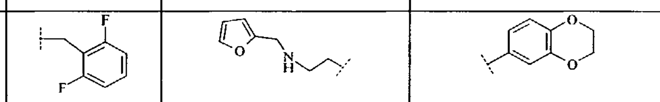
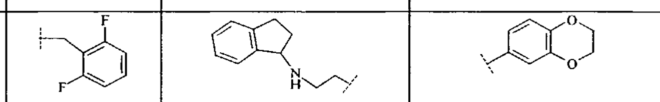
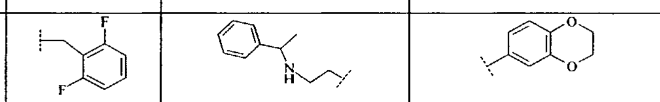
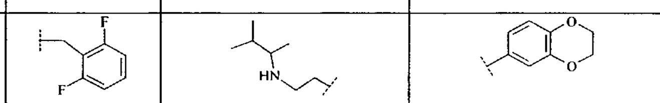
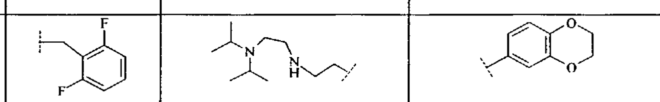
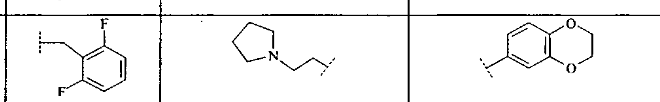
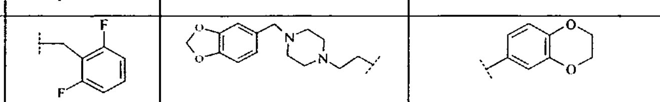
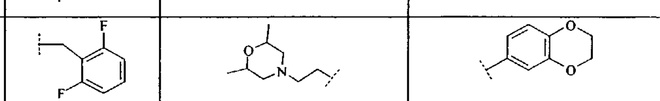
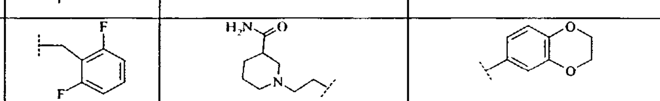
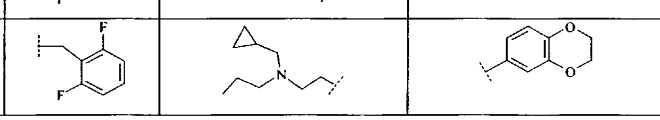
9-4	Me				485.5	486
9-5	Me				513.5	514
9-6	Me				529.5	530
9-7	Me				512.5	513
9-8	Me				518.6	519
9-9	Me				532.6	533
9-10	Me				427	428
9-11	Me				505.6	506
9-12	Me				519.6	520
9-13	Me				520.6	521
9-14	Me				534.6	535
9-15	Me				532.6	533
9-16	Me				560.6	561
9-17	Me				534.6	535
9-18	Me				534.6	535

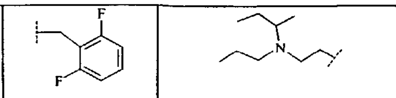
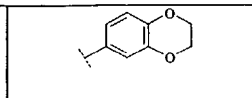
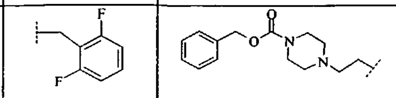
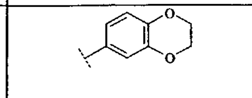
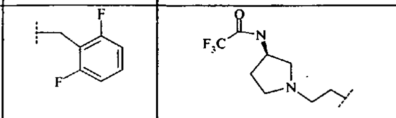
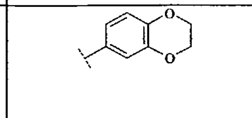
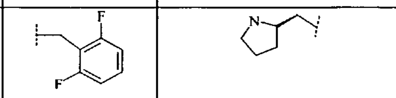
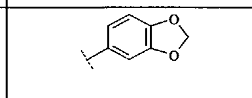
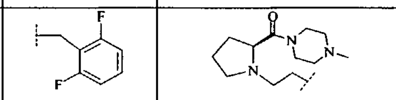
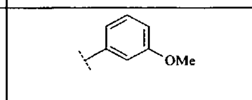
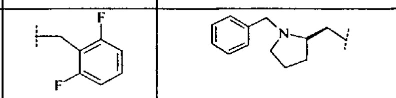
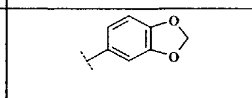
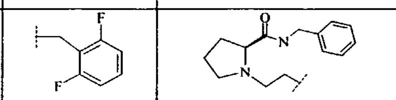
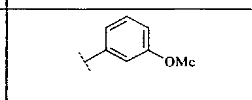
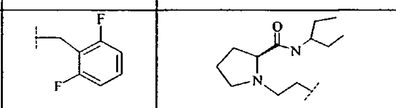
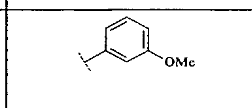
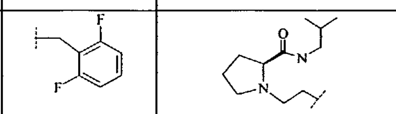
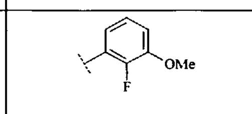
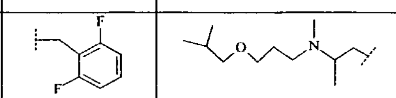
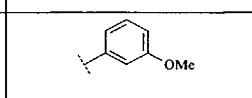
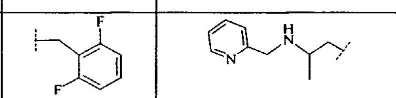
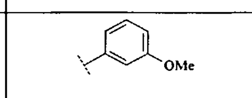
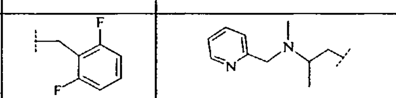
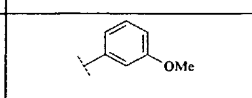
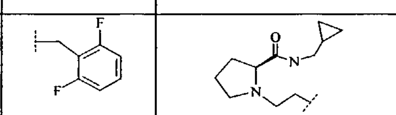
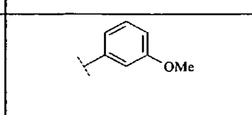
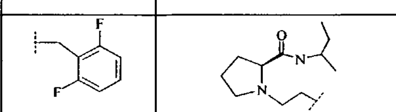
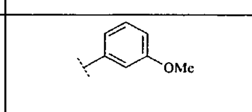
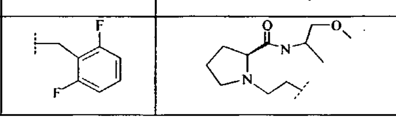
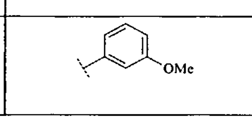
9-19	Me				529.6	530
9-20	Me				549.6	550
9-21	Me				554.6	555
9-22	Me				554.6	555
9-23	Me				575.6	576
9-24	Me				538.6	539
9-25	Me				537.6	538
9-26	Me				441.5	442
9-27	Me				546.6	547
9-28	Me				538.6	539
9-29	Me				579.6	447
9-30	Me				567.6	447
9-31	Me				533.6	534
9-32	Me				689.6	690
9-33	Me				590.7	591
9-34	Me				517.6	518

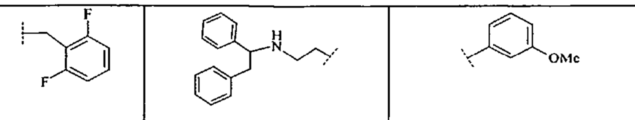
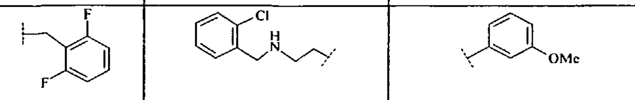
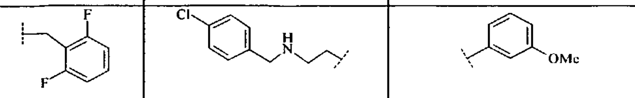
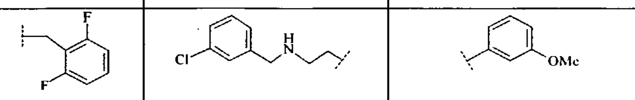
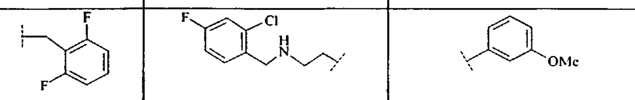
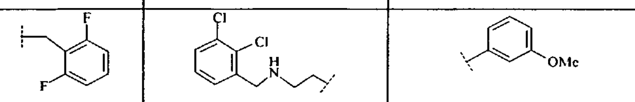
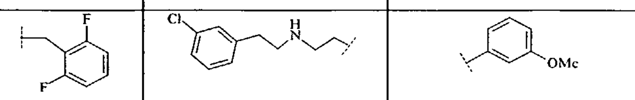
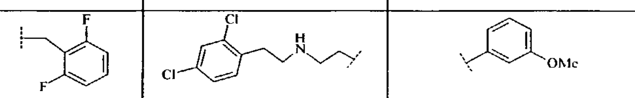
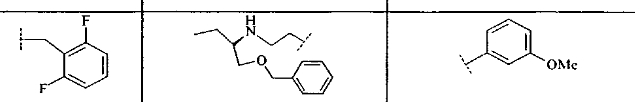
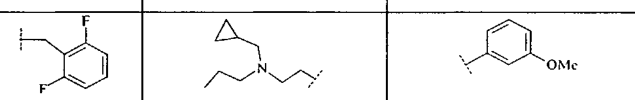
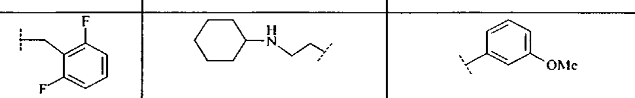
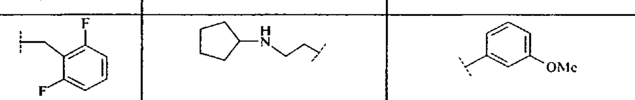
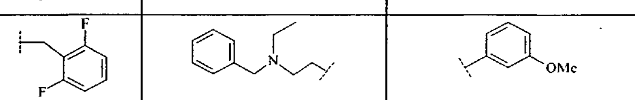
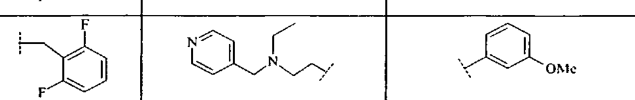
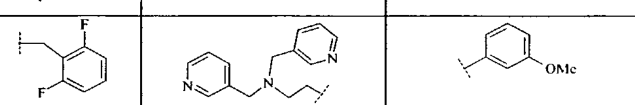
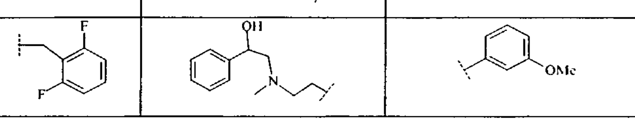
9-35	Me		666.7	667
9-36	Me		561.6	562
9-37	Me		574.6	575
9-38	Me		559.6	560
9-39	Me		643.7	644
9-40	Me		643.1	643
9-41	Me		561.7	562
9-42	Me		628.6	629
9-43	Me		666.7	667
9-44	Me		469.5	373
9-45	Me		505.5	373
9-46	Me		493.5	373
9-47	Me		459.5	373
9-48	Me		615.5	616
9-49	Me		516.6	517
9-50	Me		443.5	373

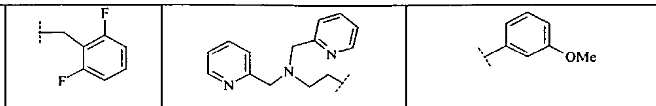
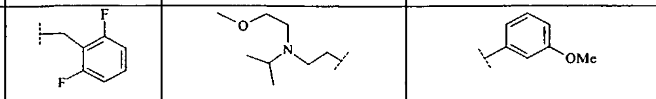
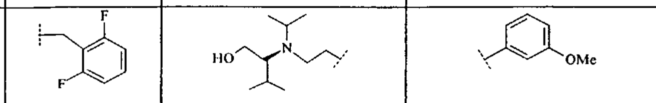
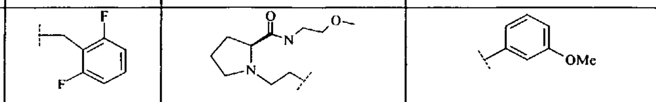
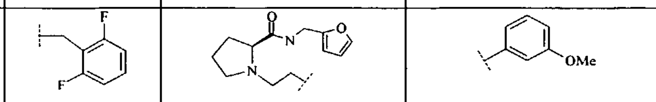
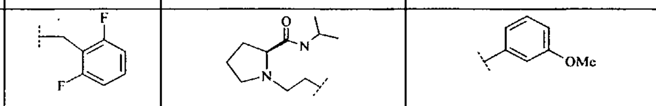
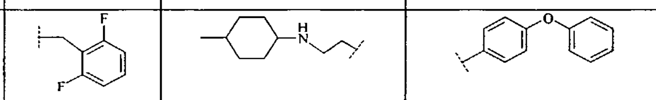
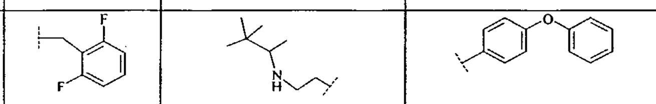
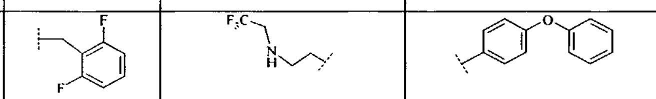
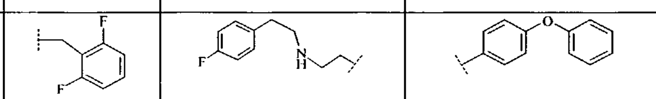
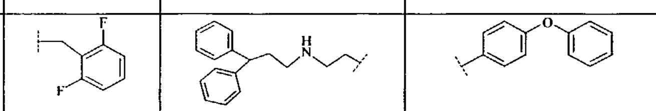
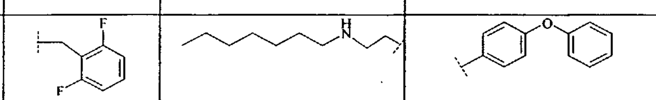
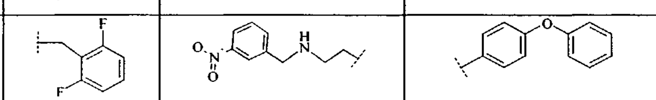
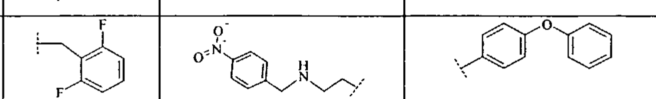
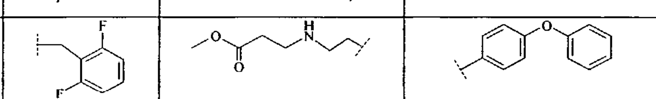
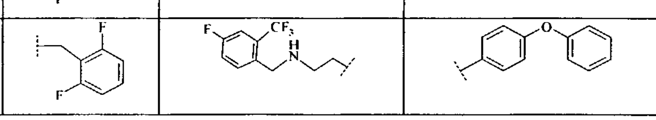
9-51	Me				592.6	593
9-52	Me				487.5	373
9-53	Me				500.5	501
9-54	Me				485.5	373
9-55	Me				569.6	372
9-56	Me				569.0	569
9-57	Me				487.6	373
9-58	Me				592.6	593
9-59	Me				495.5	399
9-60	Me				531.6	532
9-61	Me				519.5	399
9-62	Me				485.5	399
9-63	Me				641.5	642
9-64	Me				542.6	543
9-65	Me				469.5	470
9-66	Me				618.6	619

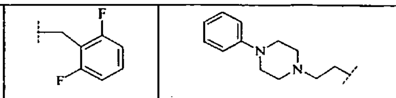
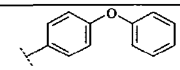
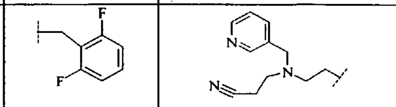
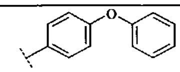
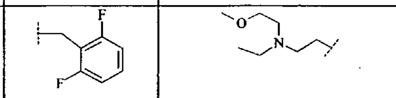
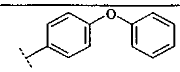
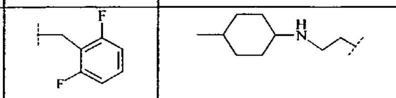
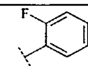
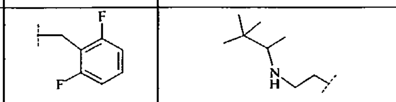
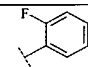
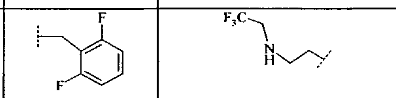
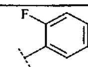
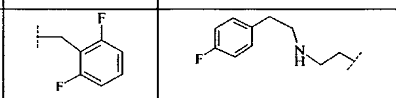
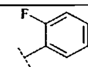
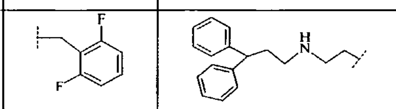
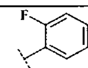
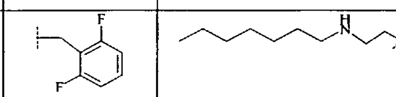
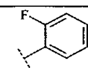
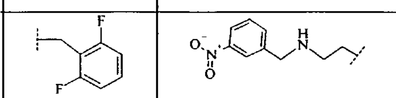
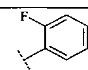
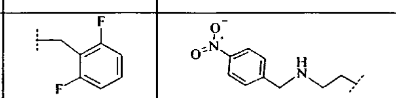
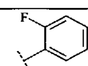
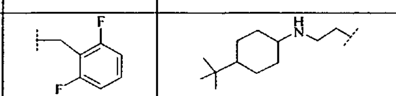
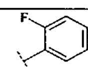
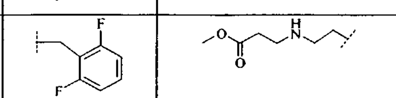
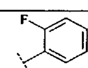
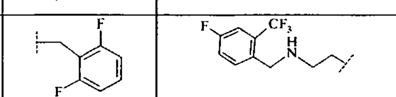
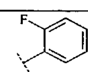
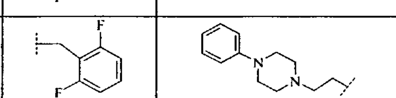
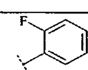
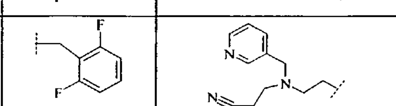
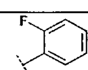
9-67	Me				513.5	514
9-68	Me				526.5	527
9-69	Me				511.6	512
9-70	Me				595.0	595
9-71	Me				513.6	399
9-72	Me				618.6	619
9-73	Me				493.6	397
9-74	Me				529.6	397
9-75	Me				517.6	397
9-76	Me				483.6	397
9-77	Me				639.6	640
9-78	Me				540.7	541
9-79	Me				467.6	468
9-80	Me				616.7	617
9-81	Me				511.6	512
9-82	Me				524.6	525

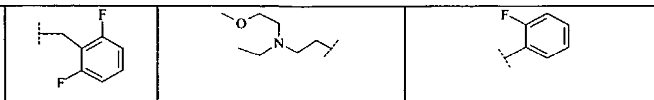
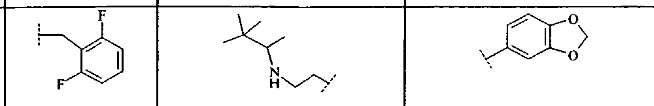
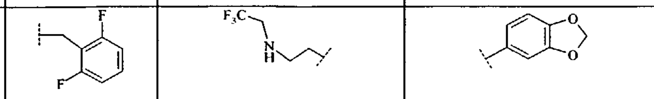
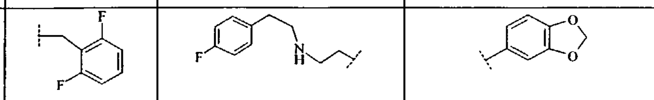
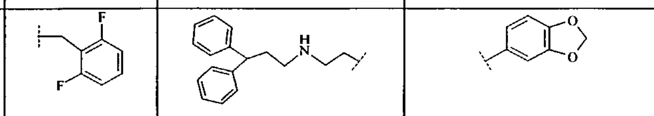
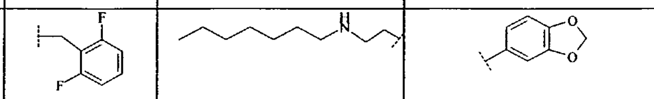
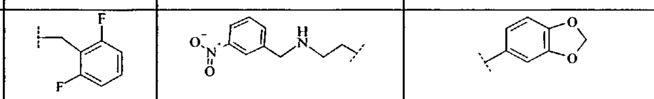
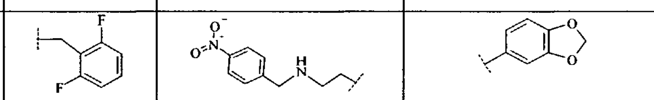
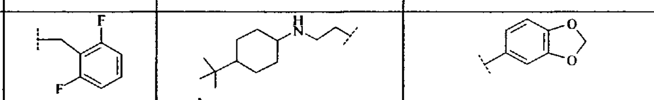
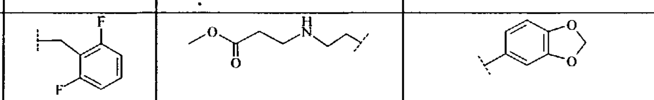
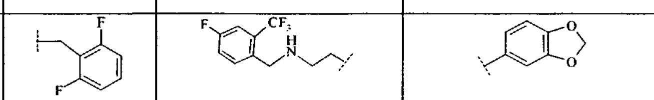
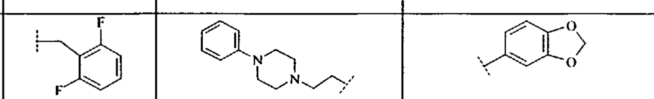
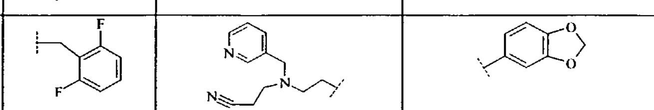
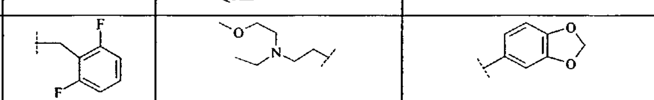
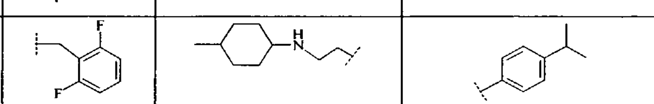
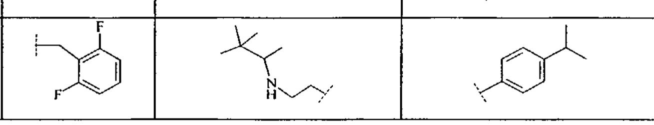
9-83	Me		509.6	510
9-84	Me		593.7	594
9-85	Me		593.1	593
9-86	Me		511.7	512
9-87	Me		578.6	579
9-88	Me		616.7	617
9-89	Me		509.5	413
9-90	Me		545.6	413
9-91	Me		533.6	413
9-92	Me		499.6	500
9-93	Me		556.6	557
9-94	Me		483.5	484
9-95	Me		632.7	633
9-96	Me		527.6	528
9-97	Me		540.6	541
9-98	Me		525.6	526

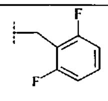
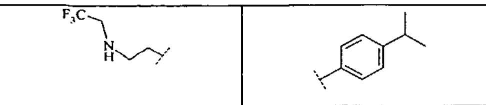
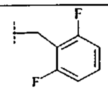
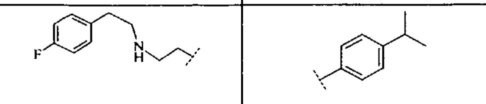
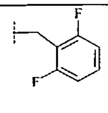
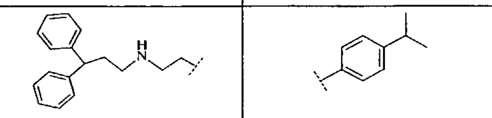
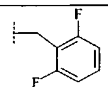
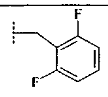
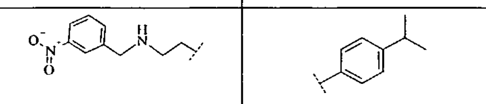
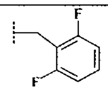
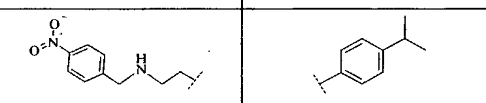
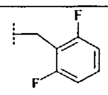
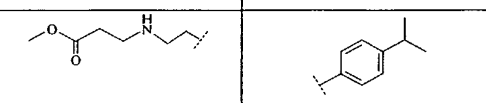
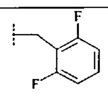
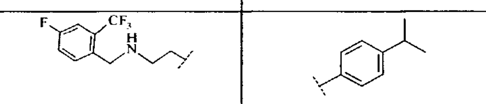
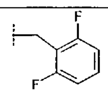
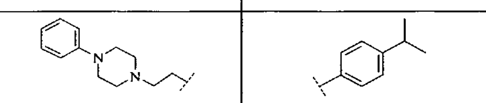
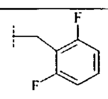
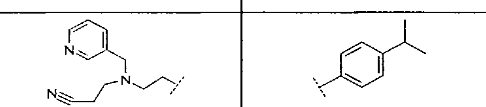
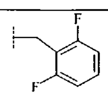
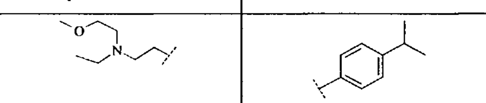
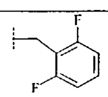
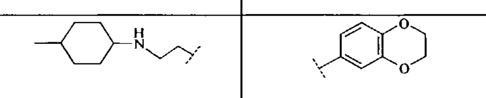
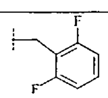
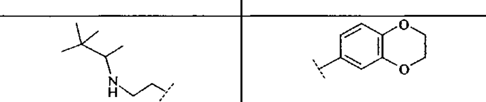
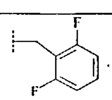
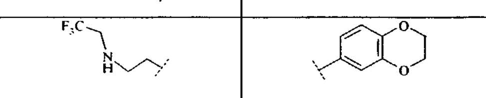
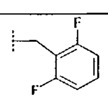
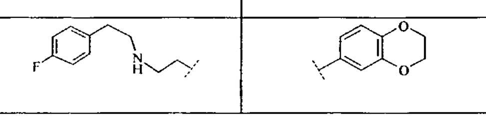
9-99	Me				527.6	528
9-100	Me				632.7	633
9-101	Me				554.5	555
9-102	Me				455.45	456
9-103	Me				581.66	
9-104	Me				545.58	546
9-105	Me				588.65	
9-106	Me				568.66	
9-107	Me				572.62	
9-108	Me				543.65	544.3
9-109	Me				506.55	507.2
9-110	Me				520.57	521.2
9-111	Me				552.61	553.3
9-112	Me				554.63	555.3
9-113	Me				570.63	571.3

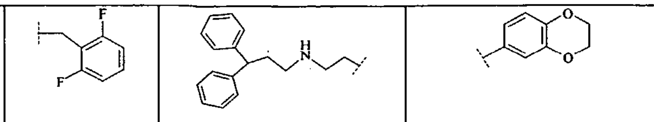
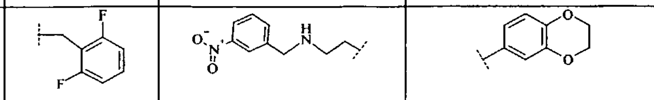
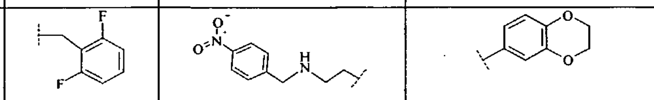
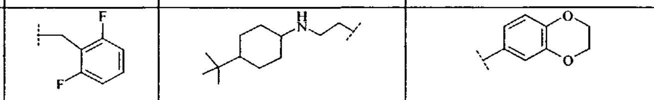
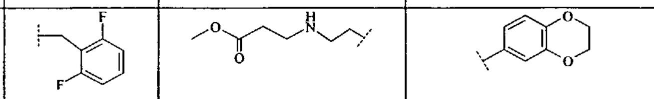
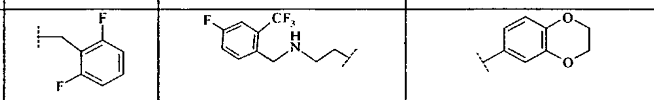
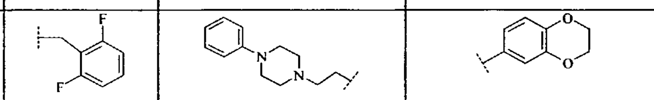
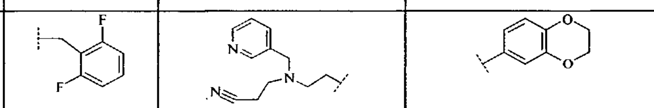
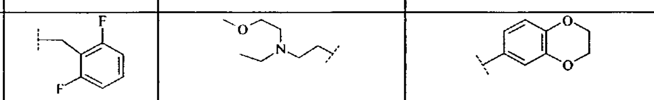
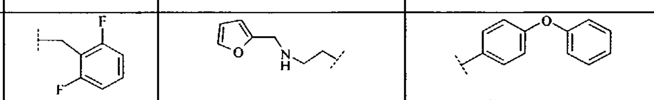
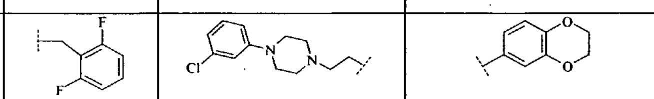
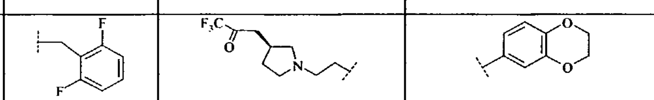
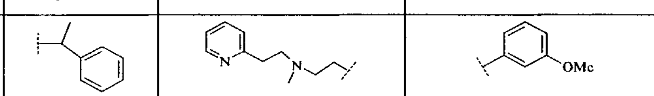
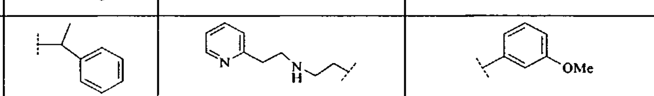
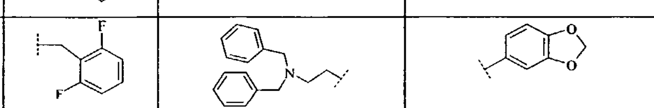
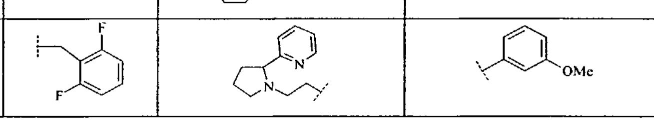
9-114	Me				581.66	582.2
9-115	Me				525.98	526.2
9-116	Me				540.00	540.2
9-117	Me				525.98	526.2
9-118	Me				543.97	544.2
9-119	Me				560.42	561.1
9-120	Me				540.00	540.2
9-121	Me				574.45	574.0
9-122	Me				563.64	564.2
9-123	Me				497.58	498.2
9-124	Me				483.55	484.2
9-125	Me				469.52	470
9-126	Me				519.58	520.2
9-127	Me				520.57	521.2
9-128	Me				583.63	584.2
9-129	Me				535.58	536.2

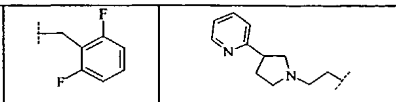
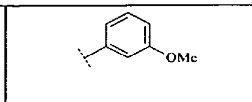
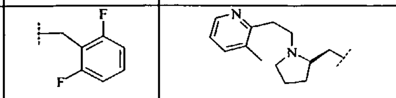
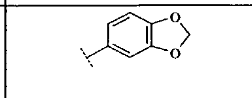
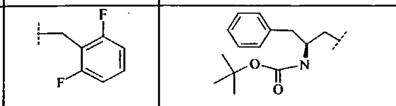
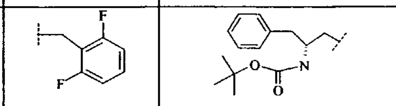
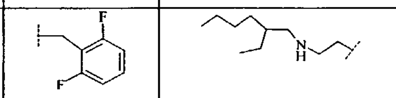
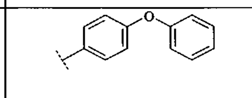
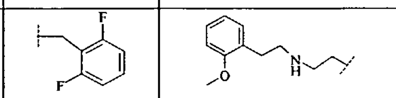
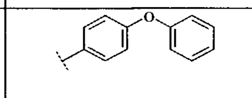
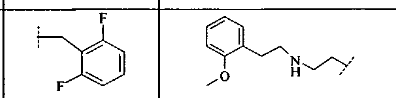
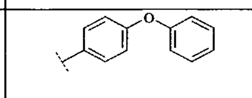
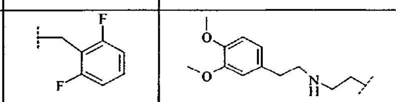
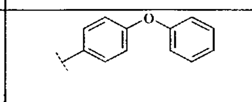
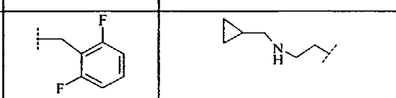
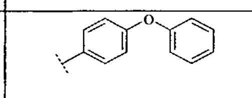
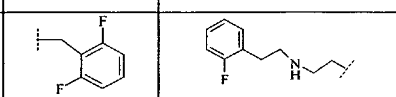
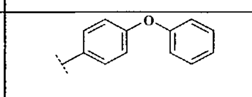
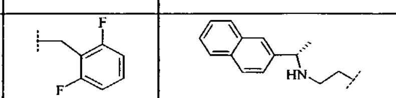
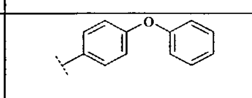
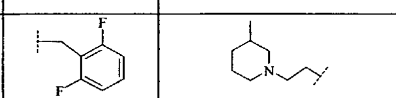
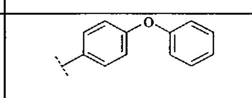
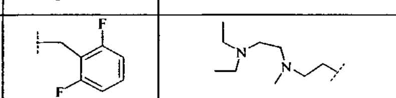
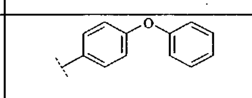
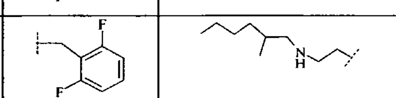
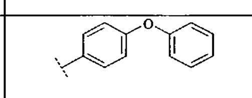
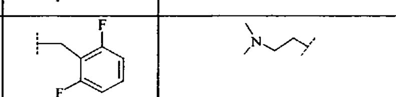
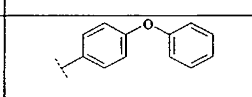
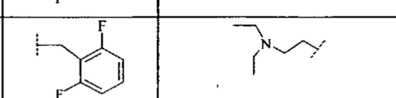
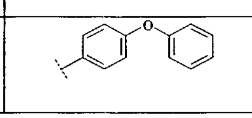
9-130	Me			583.63	584.2
9-131	Me			501.57	502.2
9-132	Me			529.62	528
9-133	Me			556.60	557
9-134	Me			578.61	578
9-135	Me			540.60	541
9-136	Me			559.65	560.4
9-137	Me			547.64	548.5
9-138	Me			545.50	546.4
9-139	Me			585.62	586.4
9-140	Me			657.75	658.4
9-141	Me			561.66	562.6
9-142	Me			598.60	599.3
9-143	Me			598.60	599.3
9-144	Me			549.57	550.4
9-145	Me			639.59	640.4

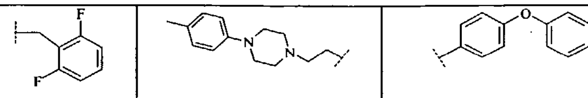
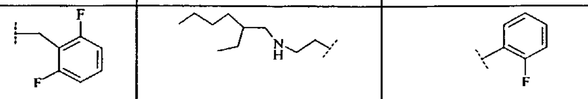
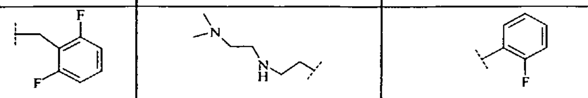
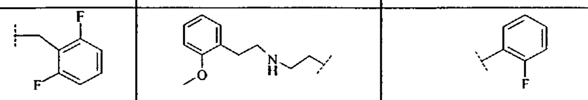
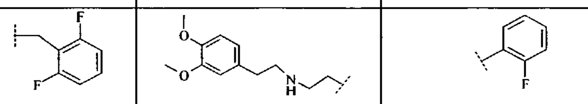
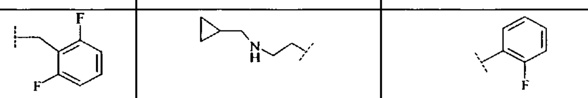
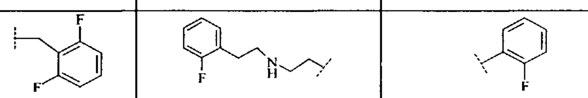
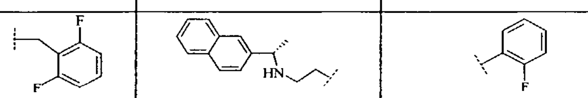
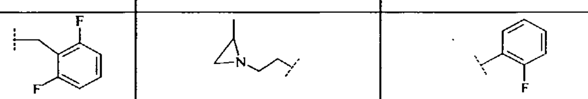
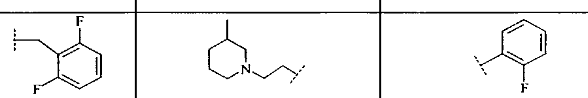
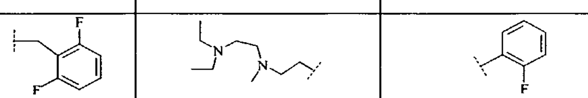
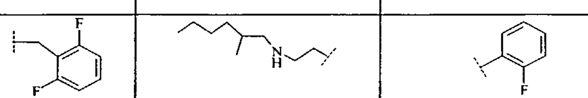
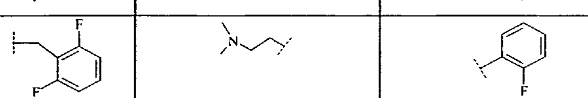
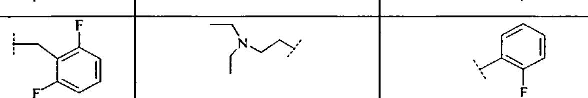
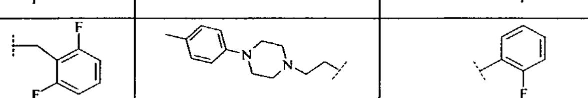
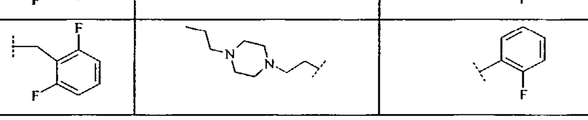
9-146	Me				608.68	609.4
9-147	Me				607.65	608.2
9-148	Me				549.61	550.4
9-149	Me				485.54	486.4
9-150	Me				473.53	474
9-151	Me				471.39	472.2
9-152	Me				511.51	512.4
9-153	Me				583.65	584.2
9-154	Me				487.56	488.2
9-155	Me				524.49	525.4
9-156	Me				524.49	525.4
9-157	Me				527.62	528.4
9-158	Me				475.46	476.3
9-159	Me				565.48	566.4
9-160	Me				534.57	535.4
9-161	Me				533.55	534.5

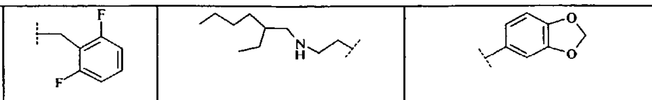
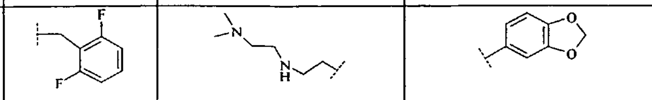
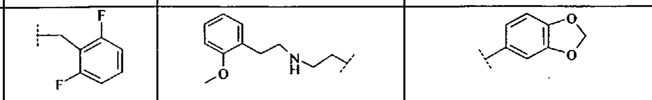
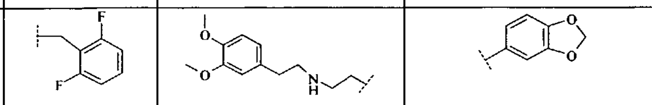
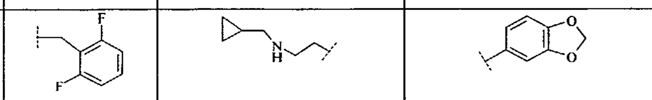
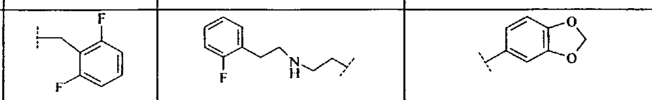
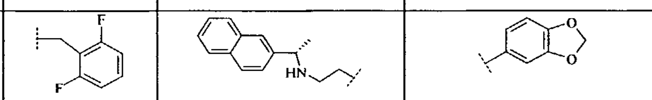
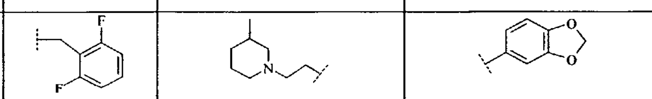
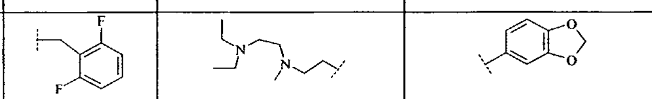
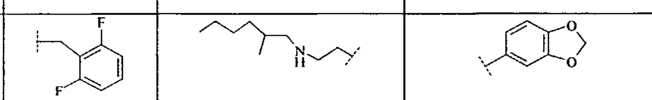
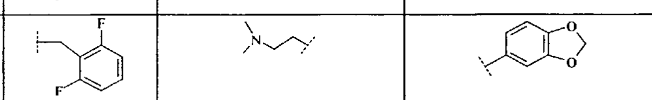
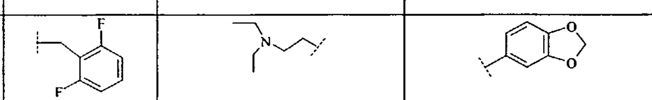
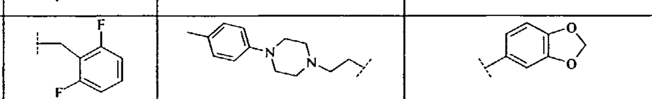
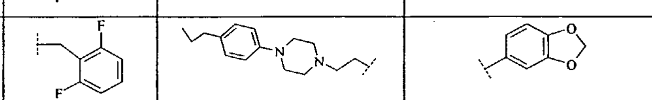
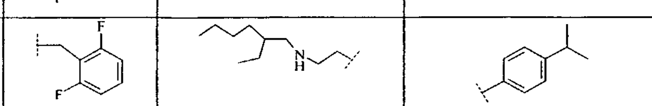
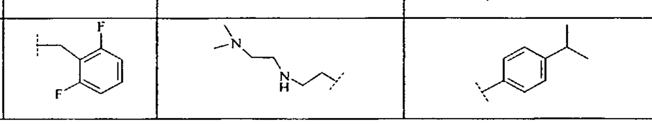
9-162	Me				475.50	476.3
9-163	Me				499.55	500.4
9-164	Me				497.41	498.3
9-165	Me				537.53	538.4
9-166	Me				609.67	610.3
9-167	Me				513.58	514.6
9-168	Me				550.51	551.3
9-169	Me				550.51	551.2
9-170	Me				553.64	554.3
9-171	Me				501.48	502.3
9-172	Me				591.50	592.4
9-173	Me				560.59	561.3
9-174	Me				559.57	560.4
9-175	Me				501.52	502.3
9-176	Me				509.63	510.6
9-177	Me				497.62	498.5

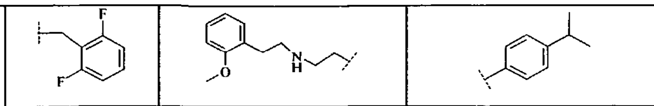
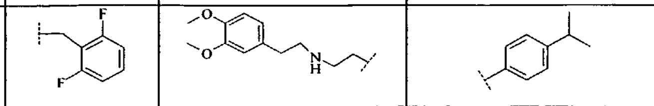
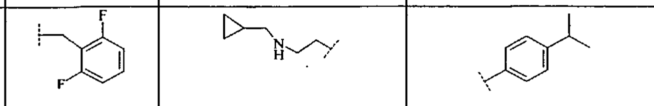
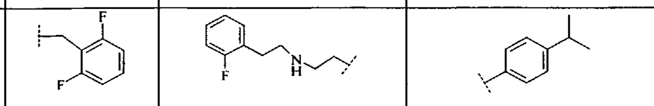
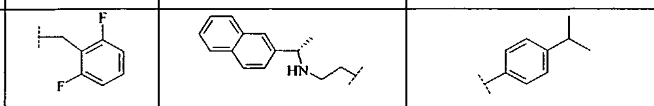
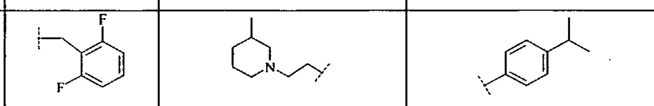
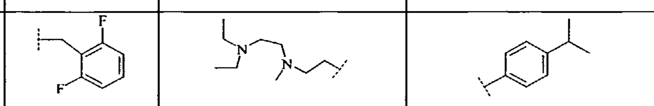
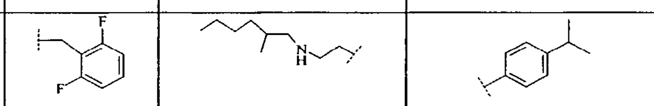
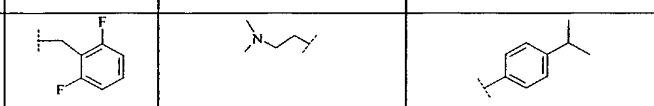
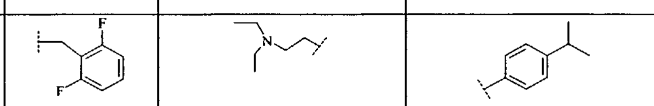
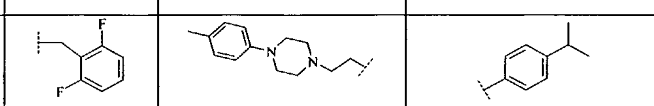
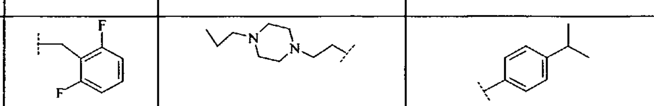
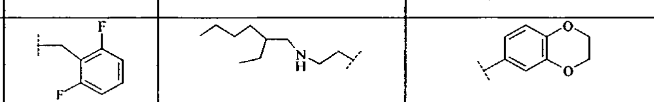
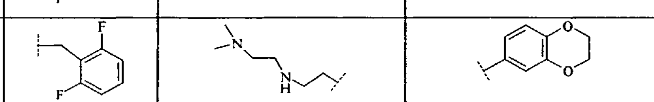
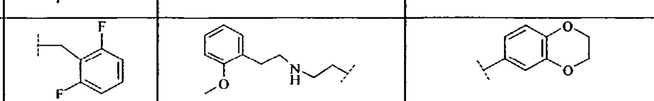
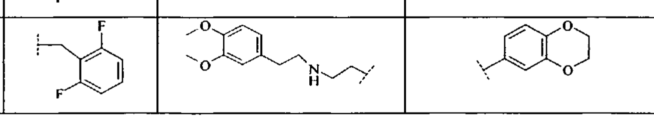
9-178	Me				495.48	496.5
9-179	Me				535.60	536.6
9-180	Me				607.74	608.4
9-181	Me				511.65	512.5
9-182	Me				548.58	549.4
9-183	Me				551.71	552.4
9-184	Me				499.55	500.4
9-185	Me				589.57	590.5
9-186	Me				558.66	559.3
9-187	Me				557.64	558.3
9-188	Me				499.59	500.4
9-189	Me				525.59	526.4
9-190	Me				513.58	514.2
9-191	Me				511.44	512.5
9-192	Me				551.56	552.3

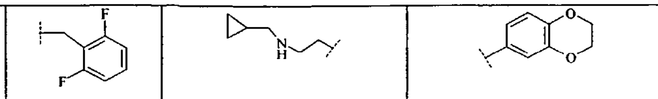
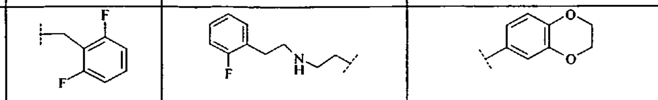
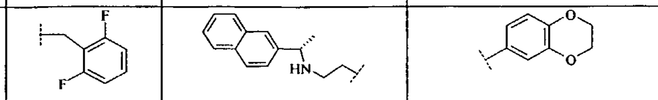
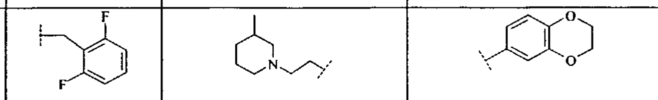
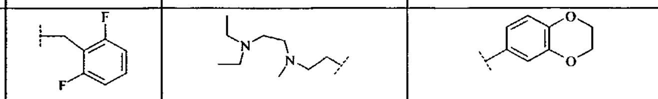
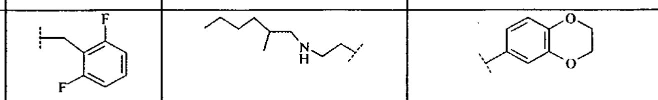
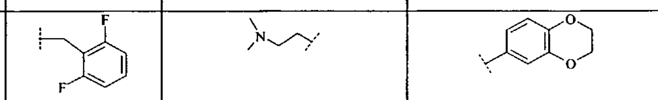
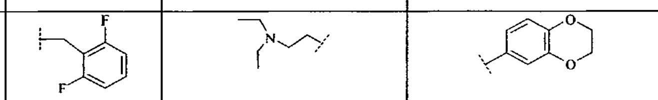
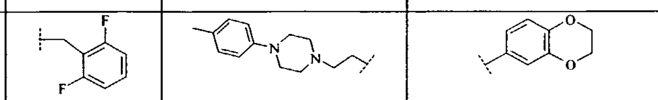
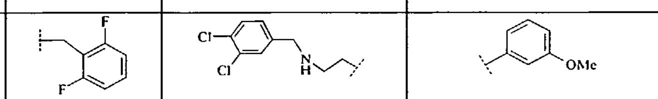
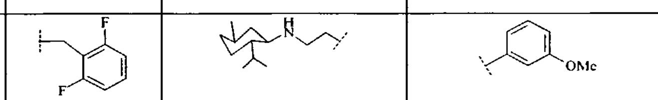
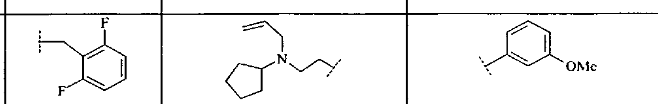
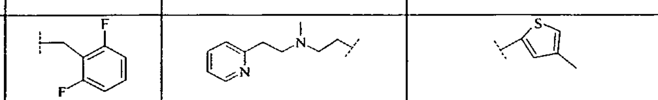
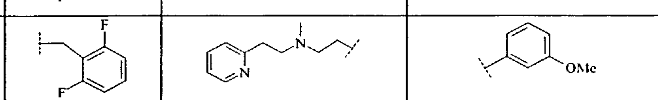
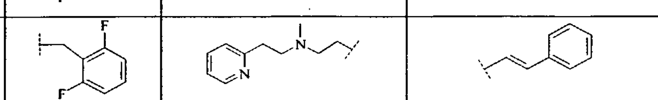
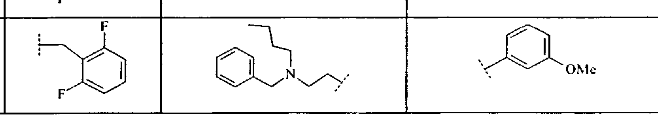
9-193	Me				623.69	624.4
9-194	Me				564.54	565.4
9-195	Me				564.54	565.4
9-196	Me				567.67	568.5
9-197	Me				515.51	516.3
9-198	Me				605.53	606.4
9-199	Me				574.6	575.4
9-200	Me				573.6	574.3
9-201	Me				515.6	516.3
9-202	Me				543.56	544.2
9-203	Me				609.07	609.2
9-204	Me				593.54	595.2
9-205	Me				498.62	499.3
9-206	Me				484.59	485.2
9-207	Me				595.64	596.4
9-208	Me				532.58	533.2

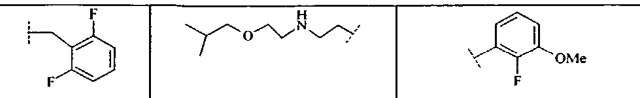
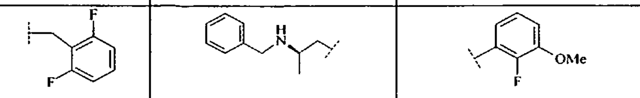
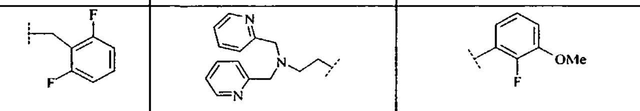
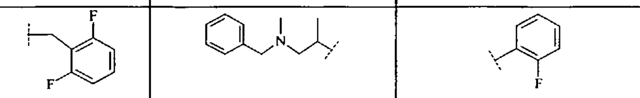
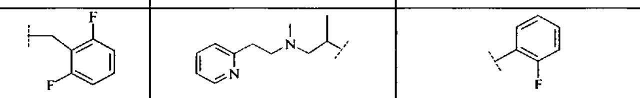
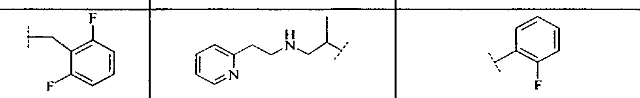
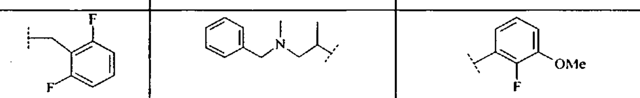
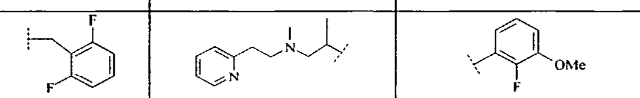
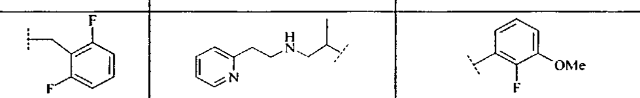
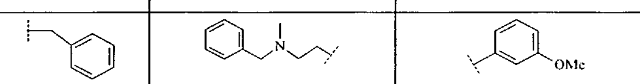
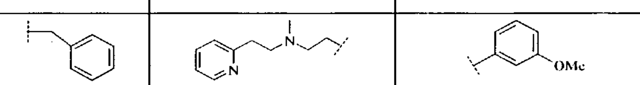
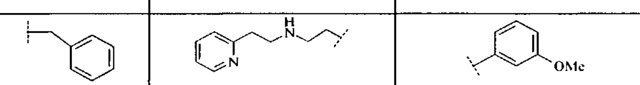
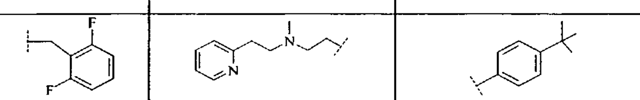
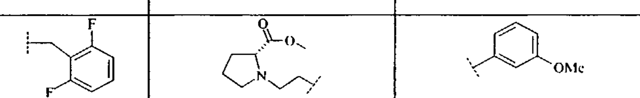
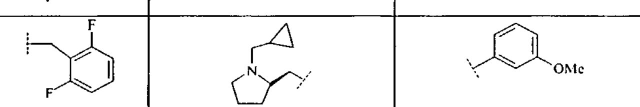
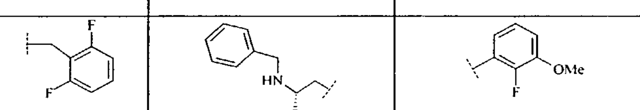
9-209	Me				532.58	533.2
9-210	Me				574.62	575
9-211	Me			Br	564.42	466/464
9-212	Me			Br	564.42	464/466
9-213	Me				575.69	576.3
9-214	Me				597.65	535.3
9-215	Me				597.65	598.2
9-216	Me				627.68	628.3
9-217	Me				517.57	518.2
9-218	Me				585.62	586.2
9-219	Me				617.69	618.2
9-220	Me				545.62	546.2
9-221	Me				576.68	577.3
9-222	Me				533.61	534.2
9-223	Me				491.53	492.2
9-224	Me				519.58	520.2

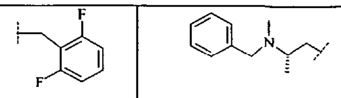
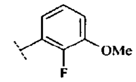
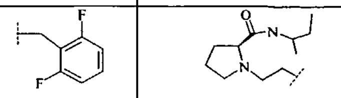
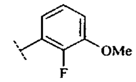
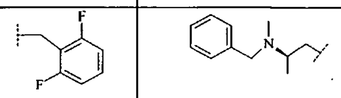
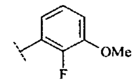
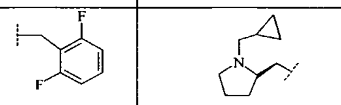
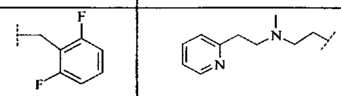
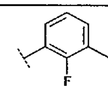
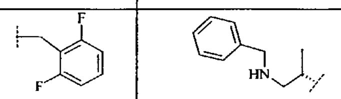
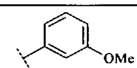
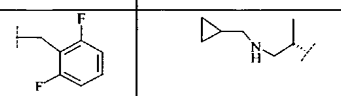
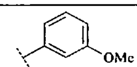
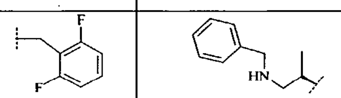
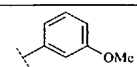
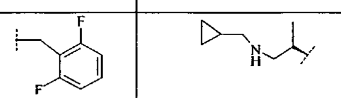
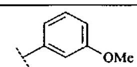
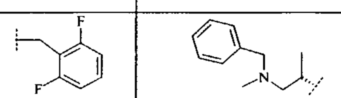
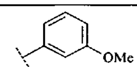
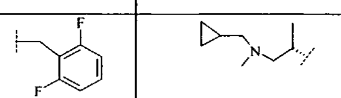
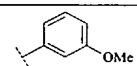
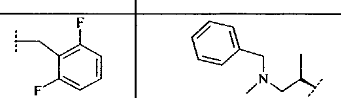
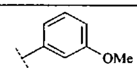
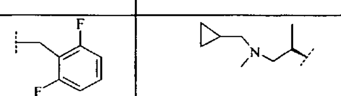
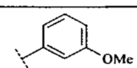
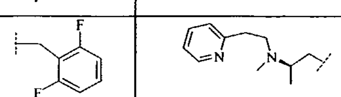
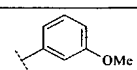
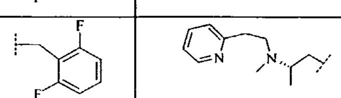
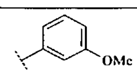
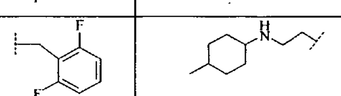
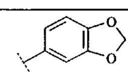
9-225	Me				622.71	623.3
9-226	Me				501.59	502.3
9-227	Me				460.49	461.2
9-228	Me				523.55	524.2
9-229	Me				553.57	554.2
9-230	Me				443.46	444.2
9-231	Me				511.51	512.2
9-232	Me				543.58	544.2
9-233	Me				429.44	430.1
9-234	Me				471.52	472.2
9-235	Me				502.57	503.3
9-236	Me				459.50	460.2
9-237	Me				417.42	418.1
9-238	Me				445.48	446.1
9-239	Me				548.60	549.2
9-240	Me				500.56	501.2

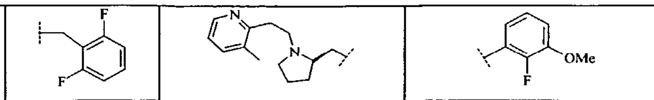
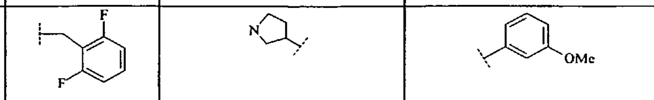
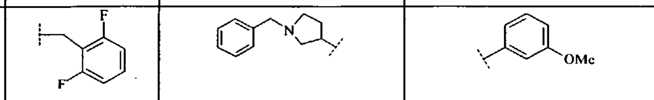
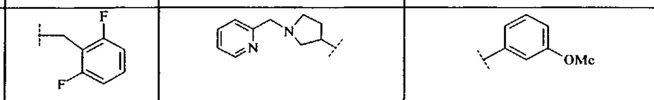
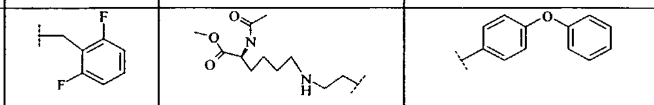
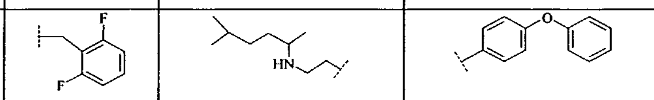
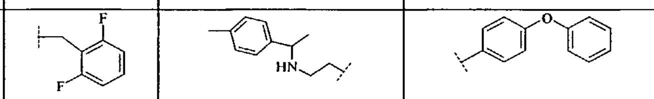
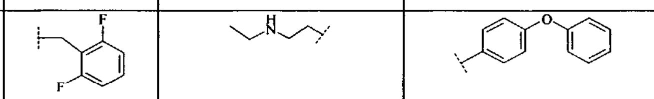
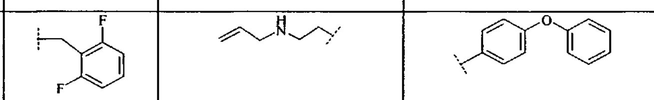
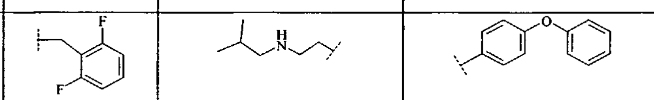
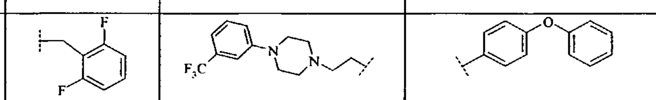
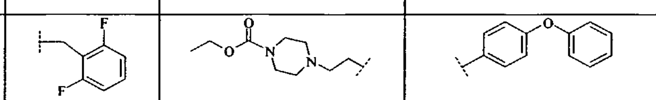
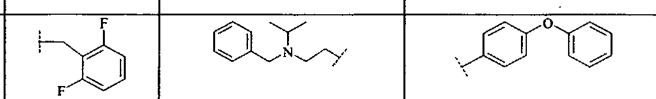
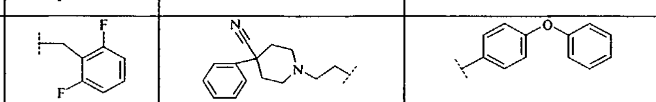
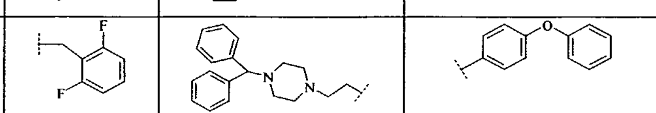
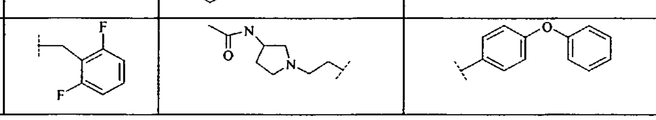
9-241	Me		527.60	528.3
9-242	Me		486.51	487.2
9-243	Me		549.57	550.2
9-244	Me		579.59	580.2
9-245	Me		469.48	470.2
9-246	Me		537.53	538.2
9-247	Me		569.60	570.2
9-248	Me		497.53	498.2
9-249	Me		528.59	529.2
9-250	Me		485.52	486.2
9-251	Me		443.44	444.1
9-252	Me		471.50	472.2
9-253	Me		574.62	575.2
9-254	Me		526.58	527.2
9-255	Me		525.68	526.3
9-256	Me		484.58	485.2

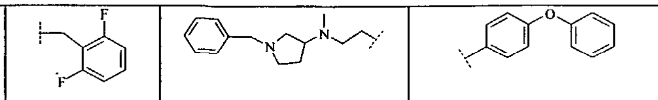
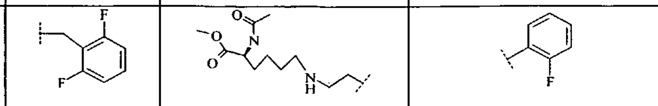
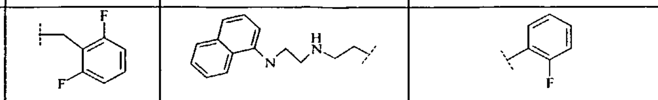
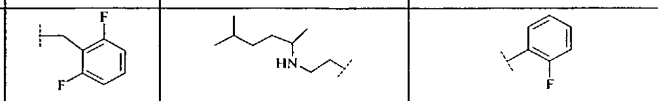
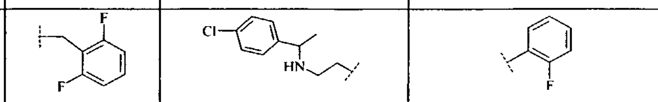
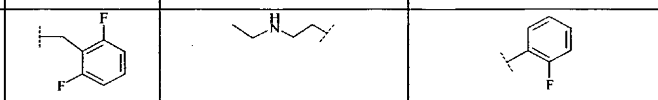
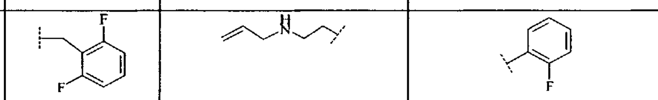
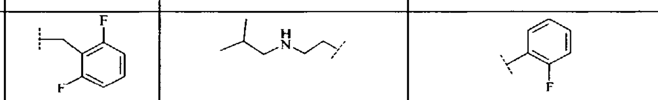
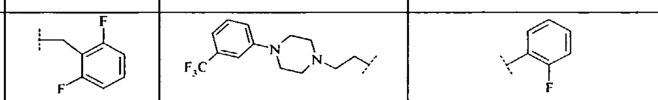
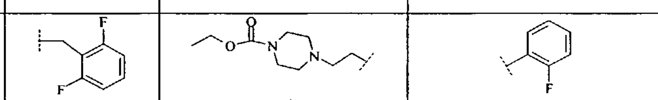
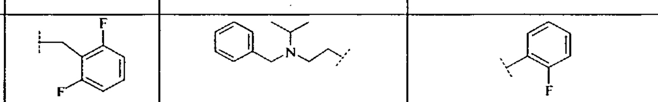
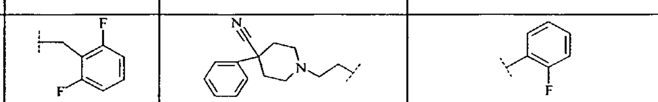
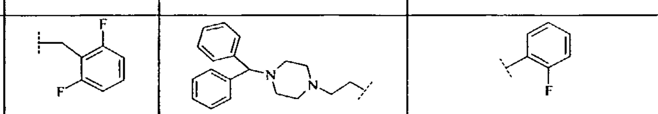
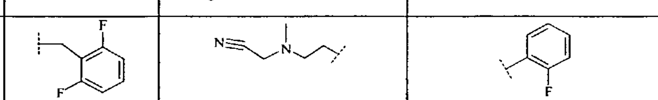
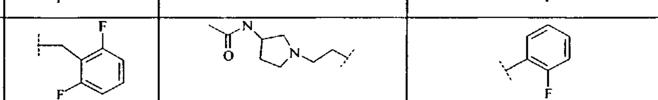
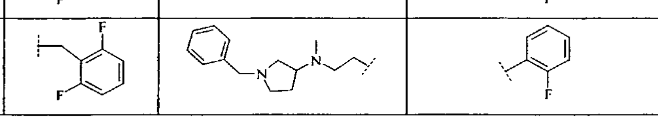
9-257	Me				547.64	548.3
9-258	Me				577.66	578.3
9-259	Me				467.55	468.2
9-260	Me				535.60	536.2
9-261	Me				567.67	568.3
9-262	Me				495.61	496.2
9-263	Me				526.66	527.3
9-264	Me				483.59	484.25
9-265	Me				441.51	442.2
9-266	Me				469.57	470.3
9-267	Me				572.69	573.3
9-268	Me				524.65	525.3
9-269	Me				541.63	542.3
9-270	Me				500.54	501.2
9-271	Me				563.59	564.2
9-272	Me				593.62	594.2

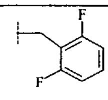
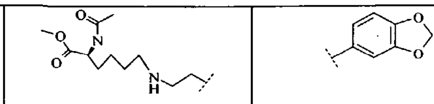
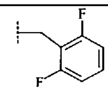
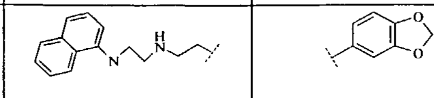
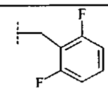
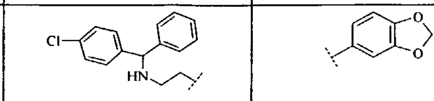
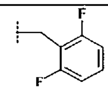
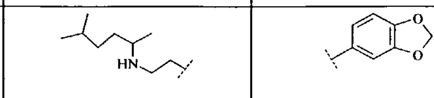
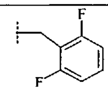
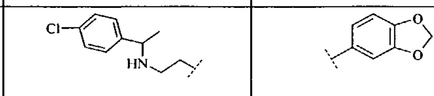
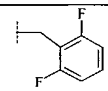
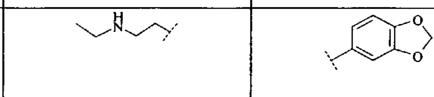
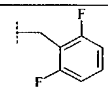
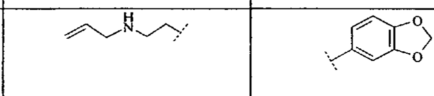
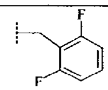
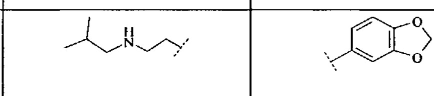
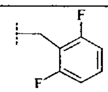
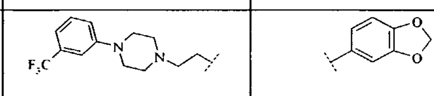
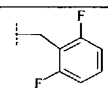
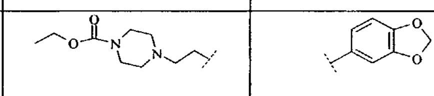
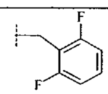
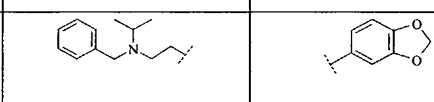
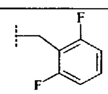
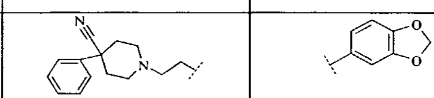
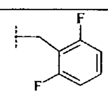
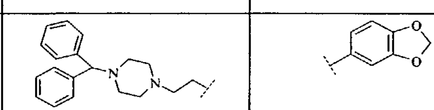
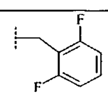
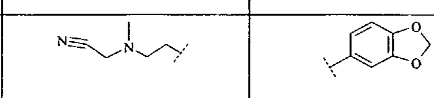
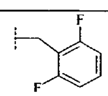
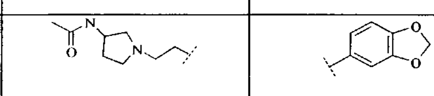
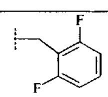
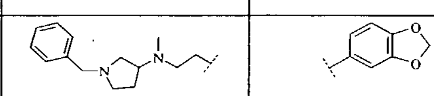
9-273	Me				483.51	484.2
9-274	Me				551.56	552.2
9-275	Me				583.63	584.2
9-276	Me				511.56	512.2
9-277	Me				542.62	543.3
9-278	Me				499.55	500.3
9-279	Me				457.47	458.2
9-280	Me				485.52	486.2
9-281	Me				588.65	589.3
9-282	Me				560.42	560
9-283	Me				539.66	540
9-284	Me				509.59	510
9-285	Me				510.60	511.5
9-286	Me				538.56	539.5
9-287	Me				516.58	517.4
9-288	Me				547.64	547

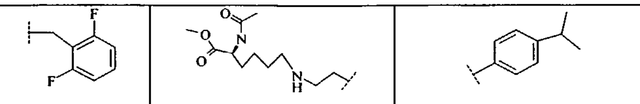
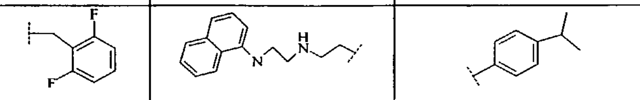
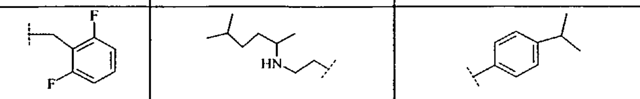
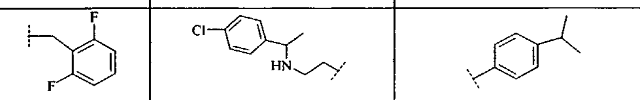
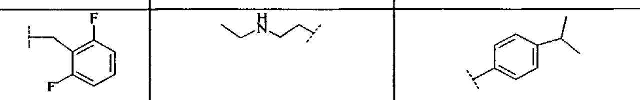
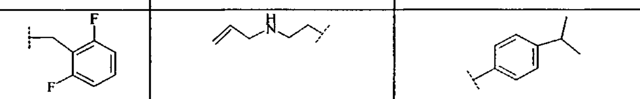
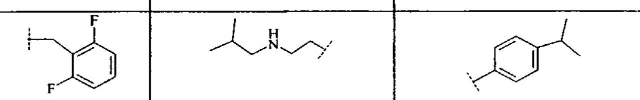
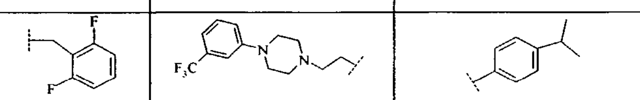
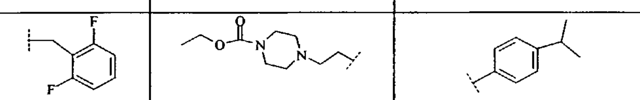
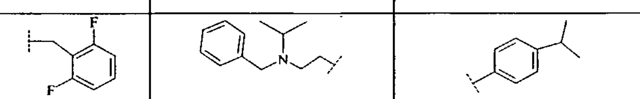
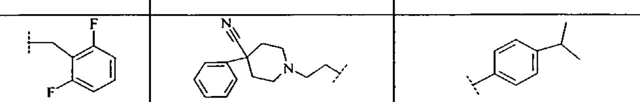
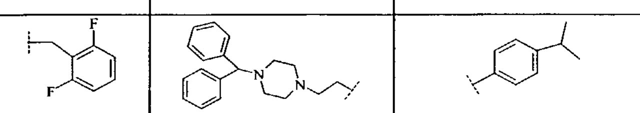
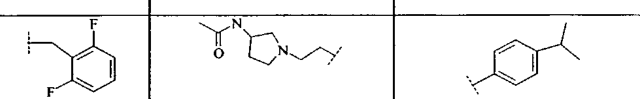
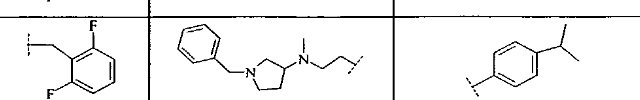
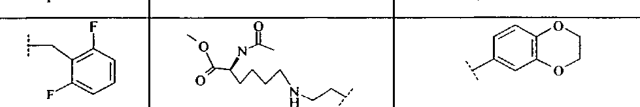
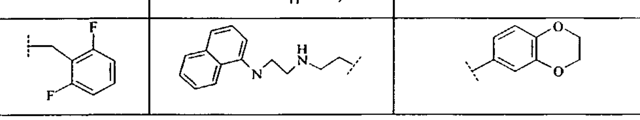
9-289	Me				519.56	534
9-290	Me				523.55	524.2
9-291	Me				615.65	616.3
9-292	Me				507.55	508.2
9-293	Me				522.56	523.6
9-294	Me				508.54	509.5
9-295	Me				537.57	538.7
9-296	Me				552.59	553.2
9-297	Me				538.56	539.5
9-298	Me				469.58	470.3
9-299	Me				484.59	485.3
9-300	Me				470.57	471.3
9-301	Me				546.65	547
9-302	Me				513.53	514
9-303	Me				495.56	496
9-304	Me				523.55	524

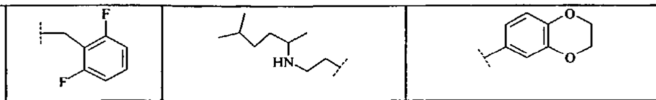
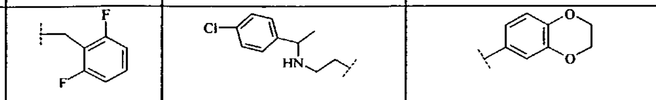
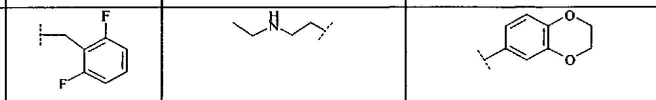
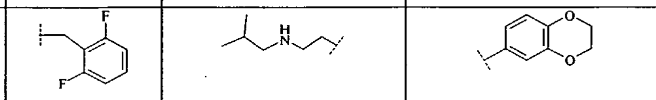
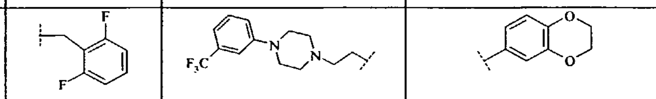
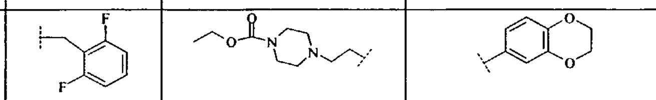
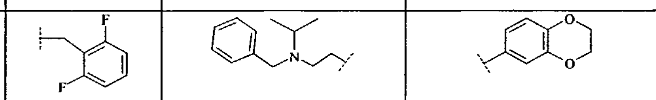
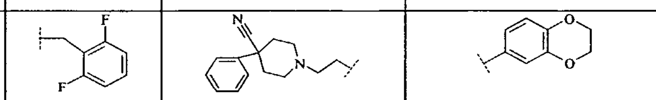
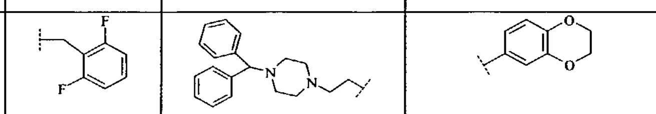
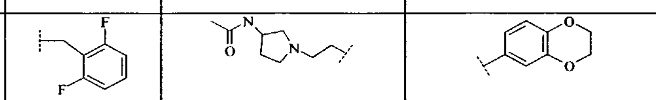
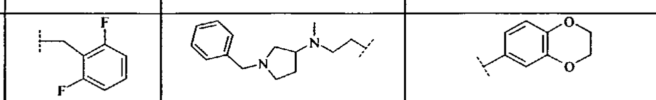
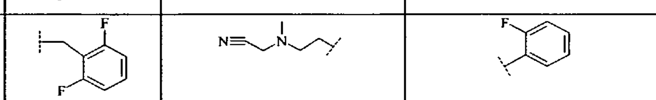
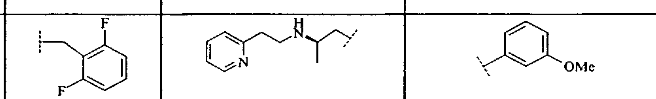
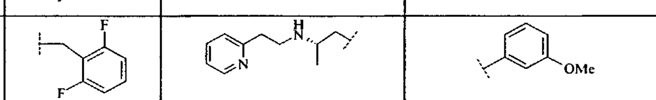
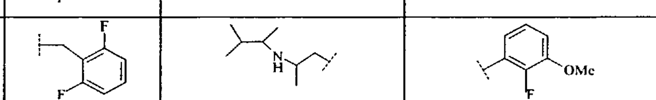
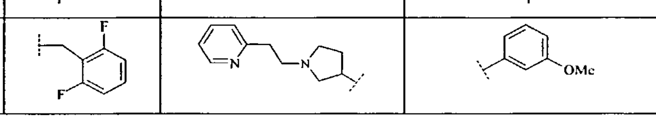
9-305	Me				537.57	538
9-306	Me				572.62	573
9-307	Me				537.57	538.3
9-308	Me			Br	505.36	505/507
9-309	Me				522.56	523
9-310	Me				505.56	506
9-311	Me				469.52	470
9-312	Me				505.56	506
9-313	Me				469.52	470
9-314	Me				519.58	520
9-315	Me				483.55	484
9-316	Me				519.58	520
9-317	Me				483.55	484
9-318	Me				534.60	535.3
9-319	Me				534.60	535.3
9-320	Me				511.56	512.5

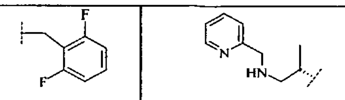
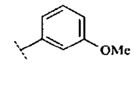
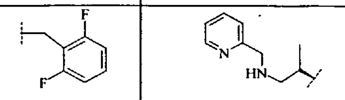
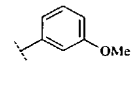
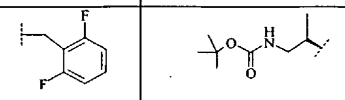
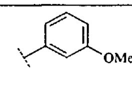
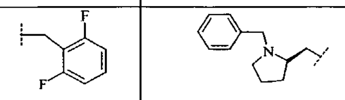
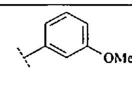
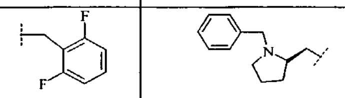
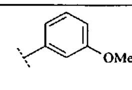
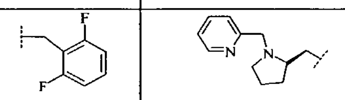
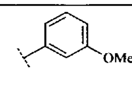
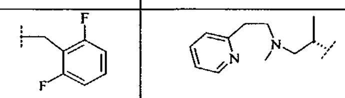
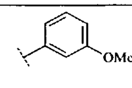
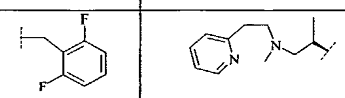
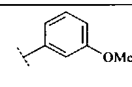
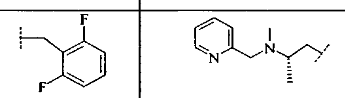
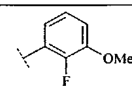
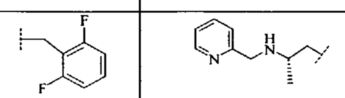
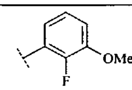
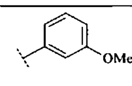
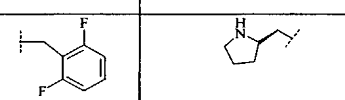
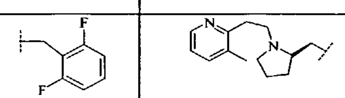
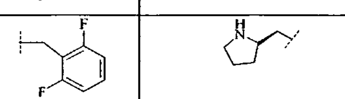
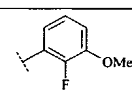
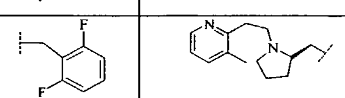
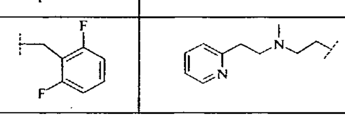
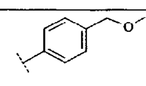
9-321	Me				578.63	598
9-322	Me				427.44	428.1
9-323	Me				517.57	518.2
9-324	Me				518.56	519.2
9-325	Me				648.70	649.5
9-326	Me				561.66	562.5
9-327	Me				602.07	447.3
9-328	Me				491.53	447.4
9-329	Me				503.54	447.3
9-330	Me				519.58	447.2
9-331	Me				676.68	677.5
9-332	Me				604.65	605.3
9-333	Me				595.68	596.4
9-334	Me				632.70	633.4
9-335	Me				698.81	699.5
9-336	Me				574.62	575.4

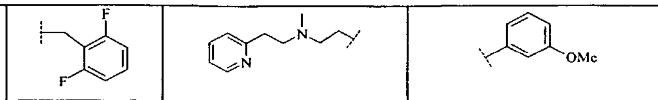
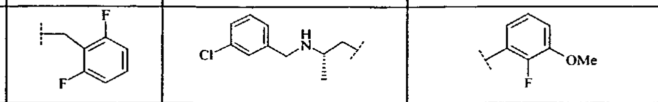
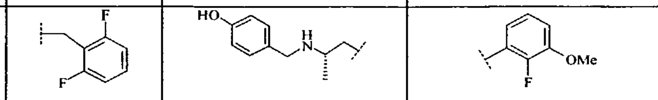
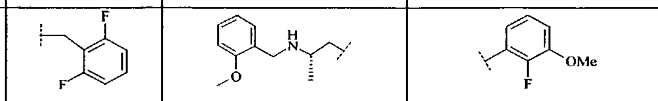
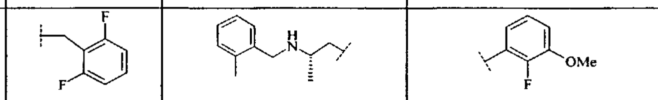
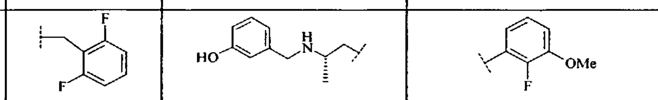
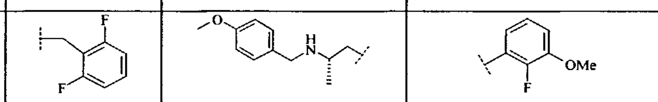
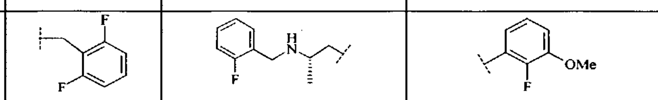
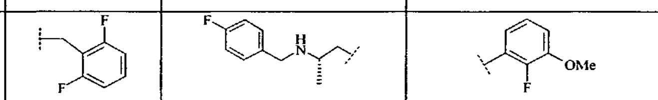
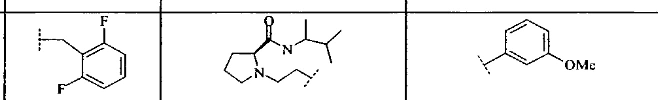
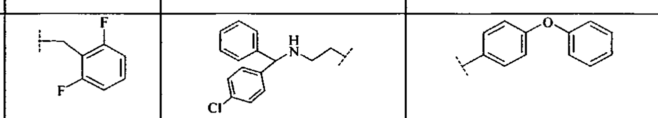
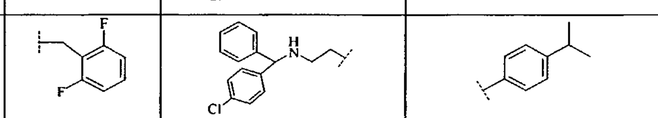
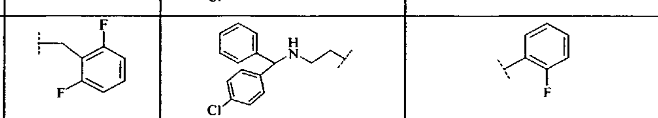
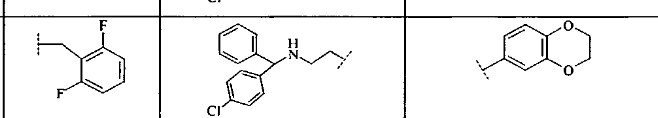
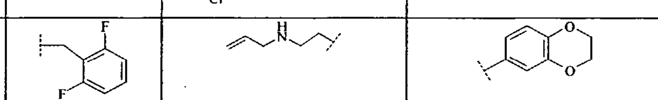
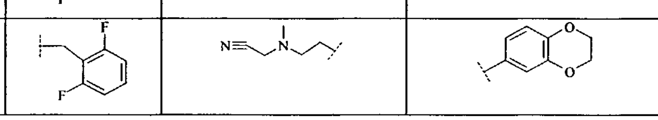
9-337	Me				636.73	637.5
9-338	Me				574.59	575.4
9-339	Me				558.60	559.3
9-340	Me				487.56	488.3
9-341	Me				527.97	373.3
9-342	Me				417.42	373.1
9-343	Me				429.44	373.3
9-344	Me				445.48	373.2
9-345	Me				602.57	603.5
9-346	Me				530.54	531.3
9-347	Me				521.58	373.1
9-348	Me				558.60	559.3
9-349	Me				624.70	625.3
9-350	Me				442.43	373.3
9-351	Me				500.51	501.4
9-352	Me				562.63	563.4

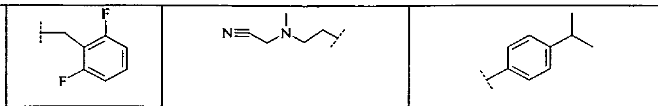
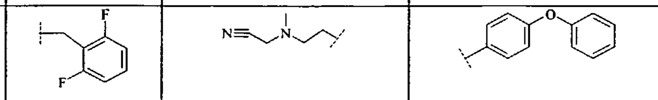
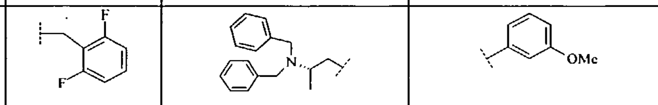
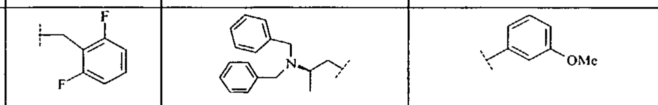
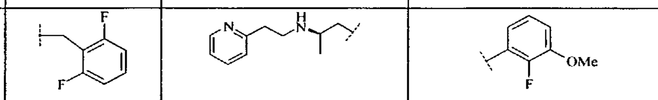
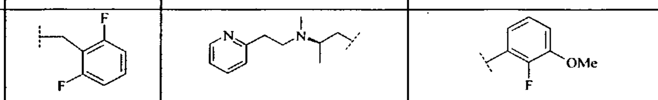
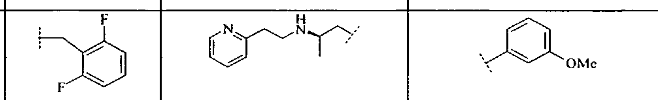
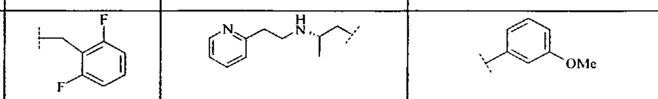
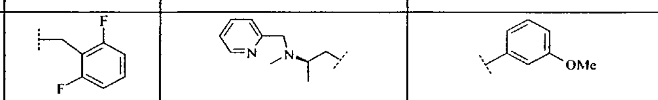
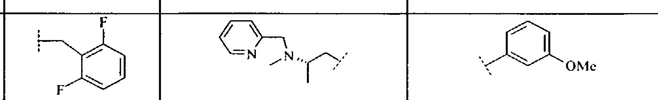
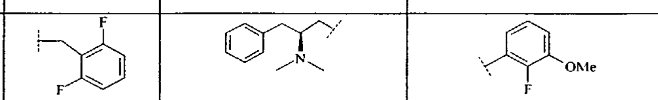
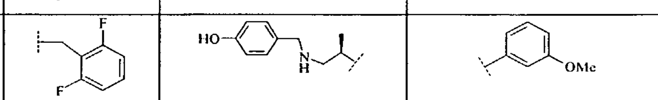
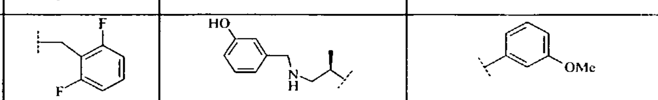
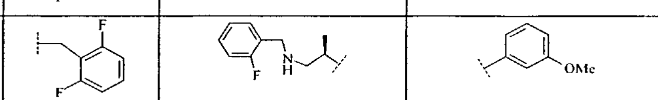
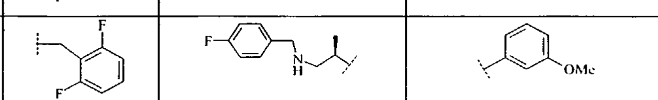
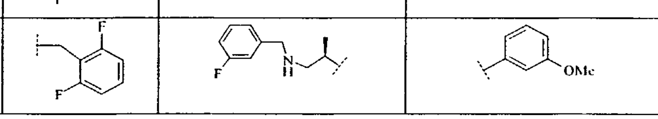
9-353	Me				600.61	601.3
9-354	Me				584.62	585.2
9-355	Me				616.06	201.3
9-356	Me				513.58	399.2
9-357	Me				553.99	399.2
9-358	Me				443.44	399.3
9-359	Me				455.45	399.2
9-360	Me				471.50	399.3
9-361	Me				628.59	629.6
9-362	Me				556.56	557.3
9-363	Me				547.59	548.5
9-364	Me				584.62	585.2
9-365	Me				650.72	651.2
9-366	Me				468.45	399.1
9-367	Me				526.53	527.3
9-368	Me				588.65	589.5

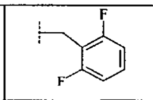
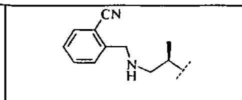
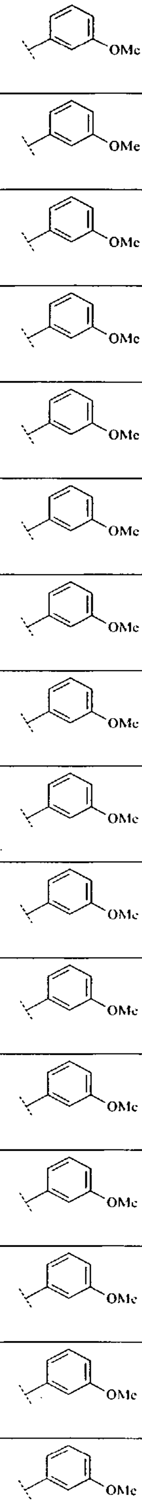
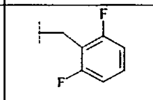
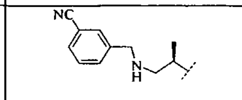
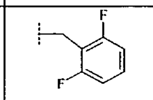
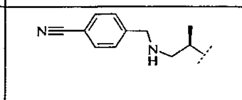
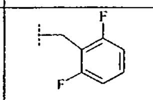
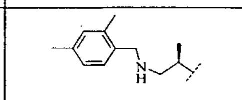
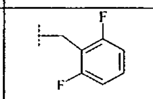
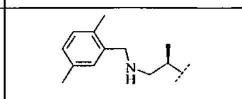
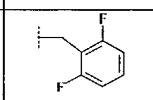
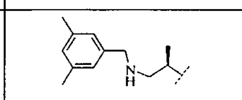
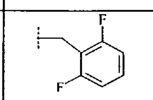
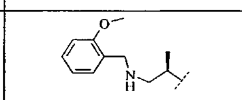
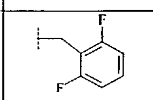
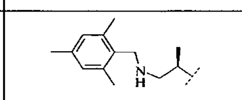
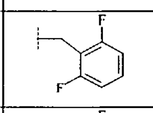
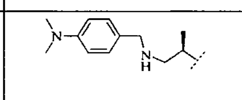
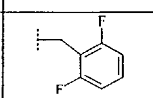
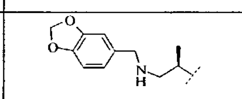
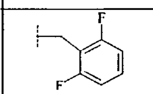
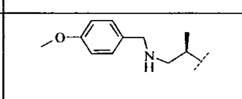
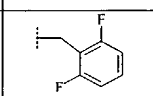
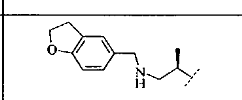
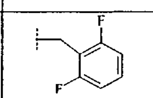
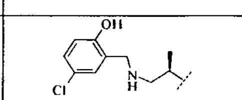
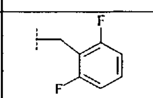
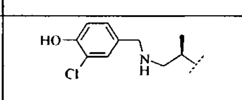
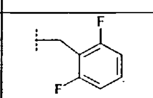
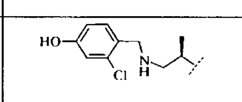
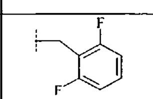
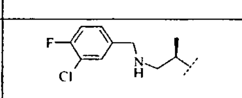
9-369	Me				598.68	599.4
9-370	Me				582.69	583.4
9-371	Me				511.65	512.5
9-372	Me				552.06	397
9-373	Me				441.51	397.1
9-374	Me				453.53	397
9-375	Me				469.57	397.1
9-376	Me				626.66	627.6
9-377	Me				554.63	555.5
9-378	Me				545.67	546.4
9-379	Me				582.69	583.3
9-380	Me				648.79	649.6
9-381	Me				524.60	525.5
9-382	Me				586.72	587.5
9-383	Me				614.64	615.5
9-384	Me				598.64	599.4

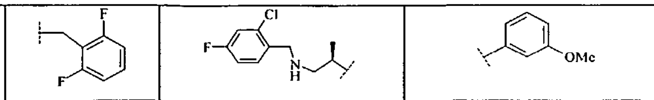
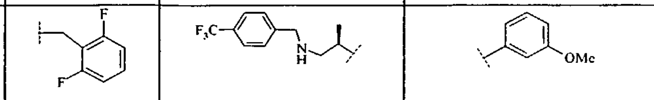
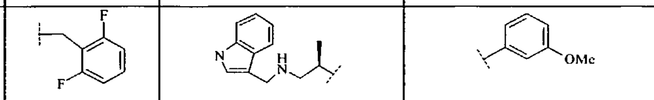
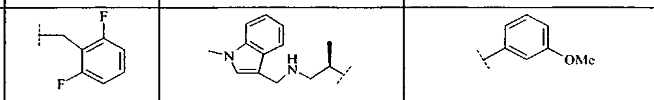
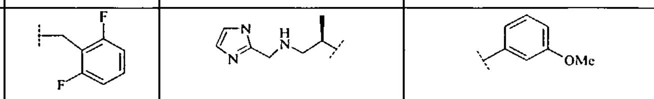
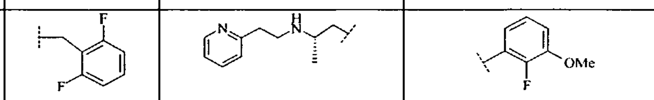
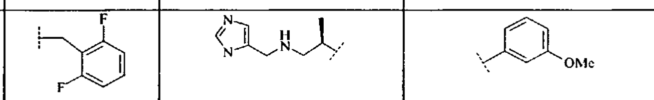
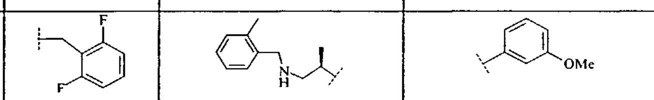
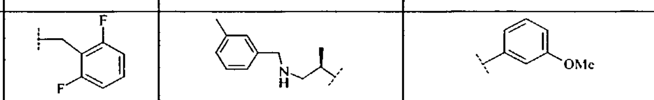
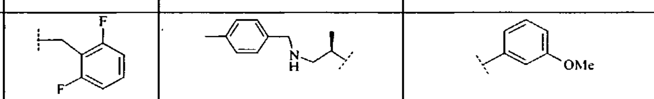
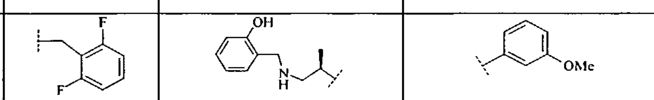
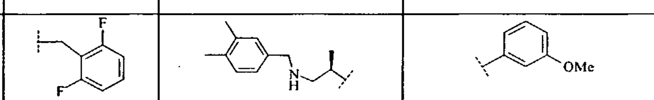
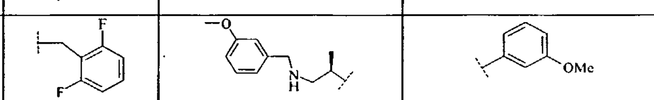
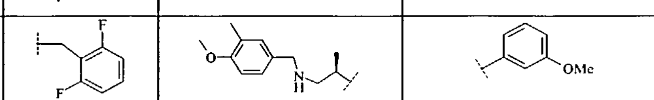
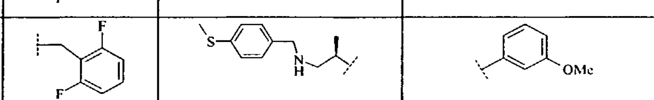
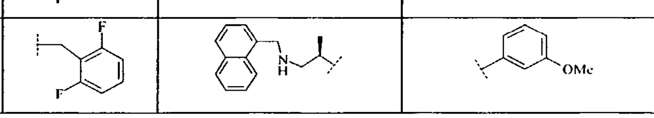
9-385	Me				527.60	528.2
9-386	Me				568.01	568.5
9-387	Me				457.47	458
9-388	Me				485.52	486.3
9-389	Me				642.62	643.7
9-390	Me				570.59	571
9-391	Me				561.62	562.5
9-392	Me				598.64	599.4
9-393	Me				664.74	665.5
9-394	Me				540.56	541.6
9-395	Me				602.67	603.6
9-396	Me				442.43	373.3
9-397	Me				520.57	521.3
9-398	Me				520.57	521.2
9-399	Me				503.56	504.2
9-400	Me				532.58	533.2

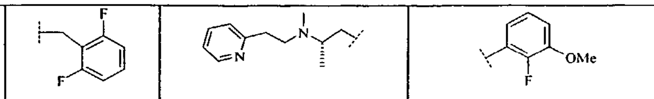
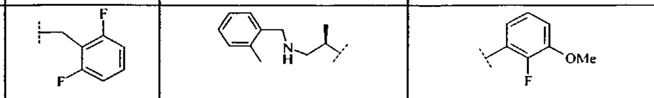
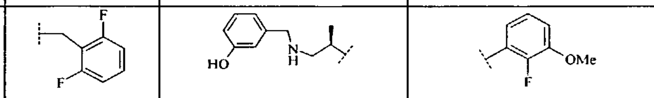
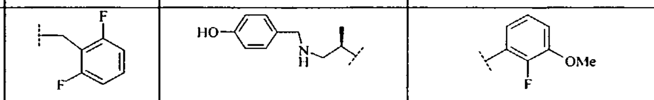
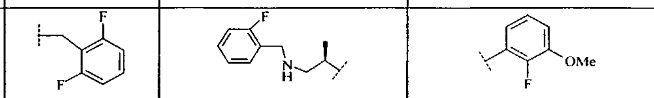
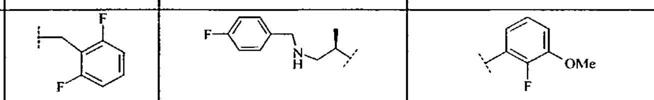
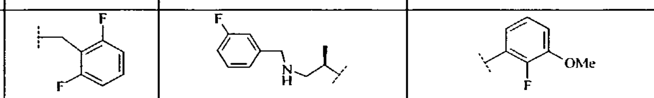
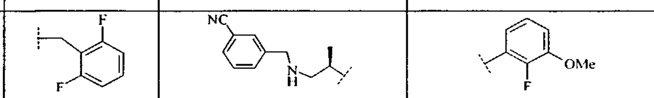
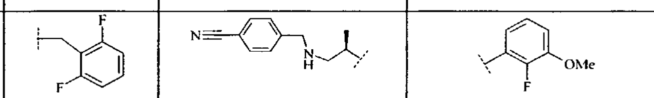
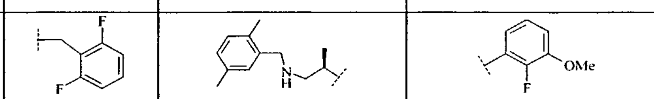
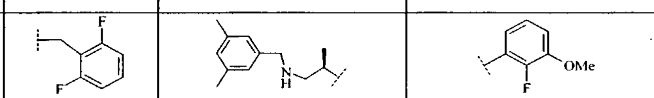
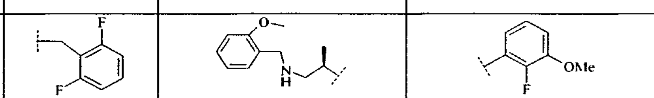
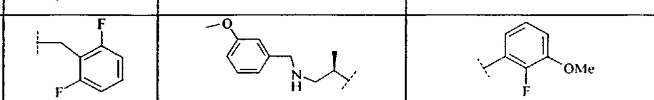
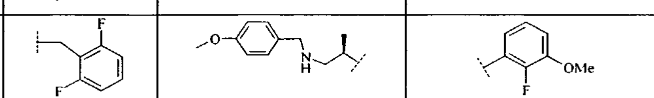
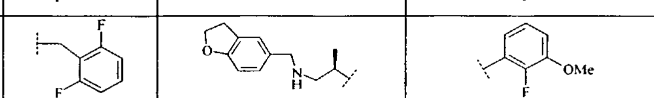
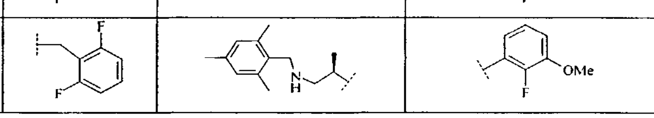
9-401	Me				506.55	507
9-402	Me				506.55	507
9-403	Me				515.55	416
9-404	Me				531.6	532
9-405	Me				549.5	550
9-406	Me				550.57	550
9-407	Me				534.60	535
9-408	Me				534.60	535
9-409	Me				538.56	539
9-410	Me				524.54	525
9-411	Me				554.63	555
9-412	Me			H	335.35	336
9-413	Me			Br	533.41	533/535
9-414	Me				459.46	460
9-415	Me			H	454.51	455
9-416	Me				534.60	535.5

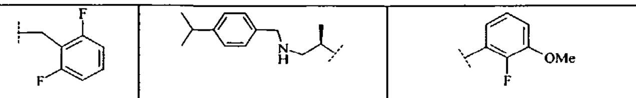
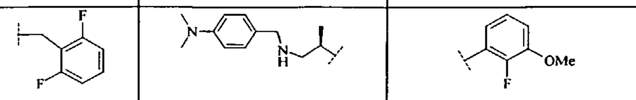
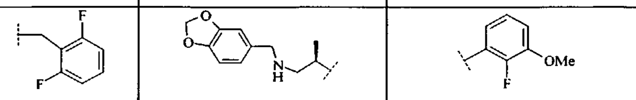
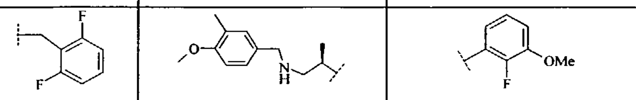
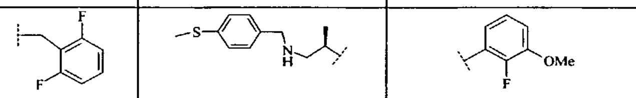
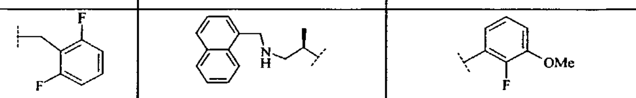
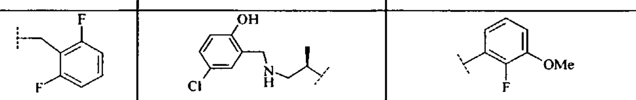
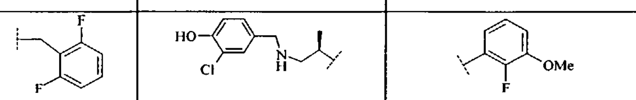
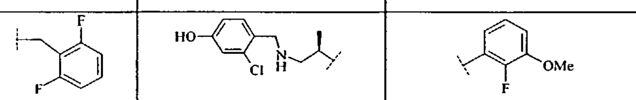
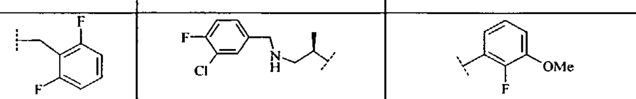
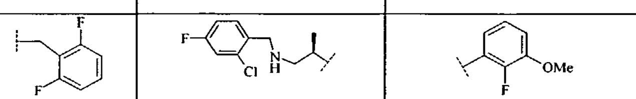
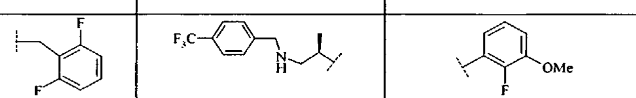
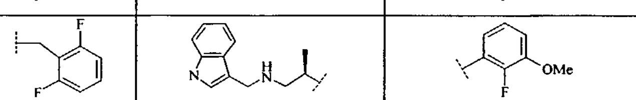
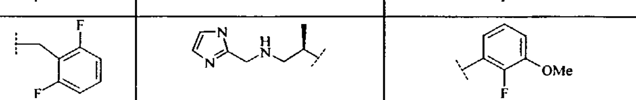
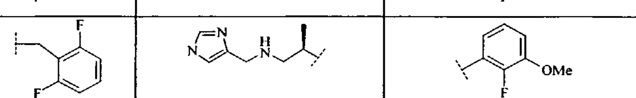
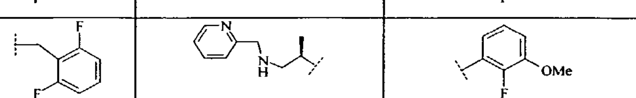
9-417	Me				520.57	521.5
9-418	Me				557.99	558
9-419	Me				539.55	540
9-420	Me				553.57	554
9-421	Me				537.57	538
9-422	Me				539.55	540
9-423	Me				553.57	554
9-424	Me				541.54	542
9-425	Me				541.54	542
9-426	Me				568.66	569
9-427	Me				664.14	664.2
9-428	Me				614.13	614.2
9-429	Me				590.04	590.2
9-430	Me				630.08	630.2
9-431	Me				469.48	470.2
9-432	Me				482.48	483.1

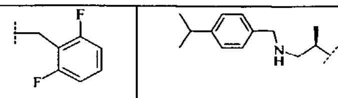
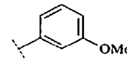
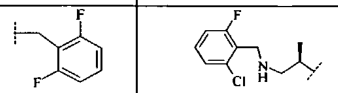
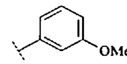
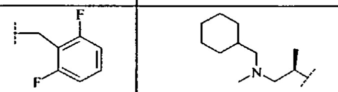
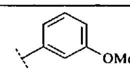
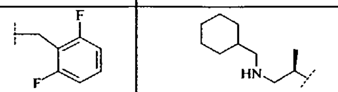
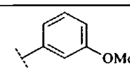
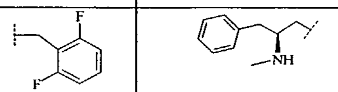
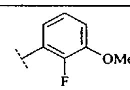
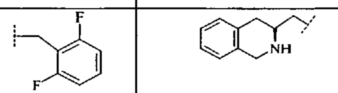
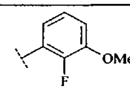
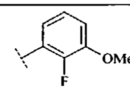
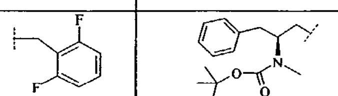
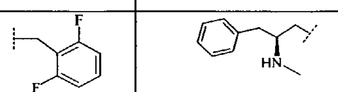
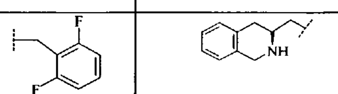
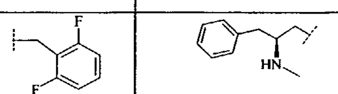
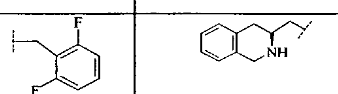
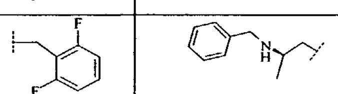
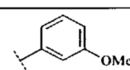
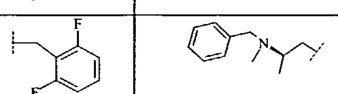
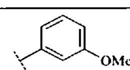
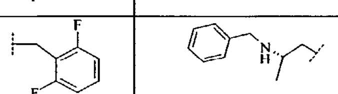
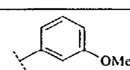
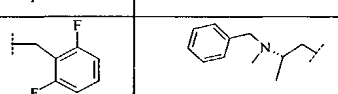
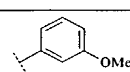
9-433	Me				466.52	467.2
9-434	Me				516.54	517.2
9-435	Me				595.68	596.3
9-436	Me				595.68	596.3
9-437	Me				538.56	539.2
9-438	Me				552.59	553.3
9-439	Me				506.55	507.2
9-440	Me				506.55	507.2
9-441	Me				520.57	521.2
9-442	Me				520.57	521.2
9-443	Me				537.57	538
9-444	Me				521.56	522.2
9-445	Me				521.56	522.2
9-446	Me				523.55	524.2
9-447	Me				523.55	524.2
9-448	Me				523.55	524.2

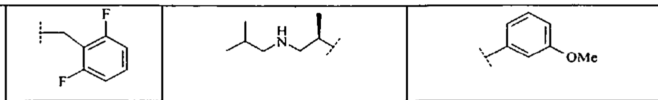
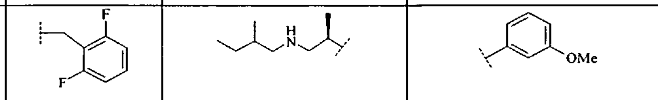
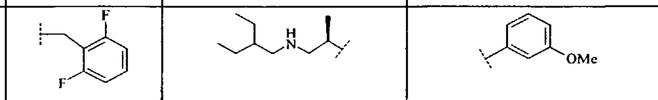
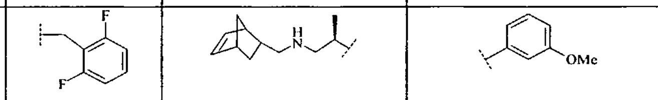
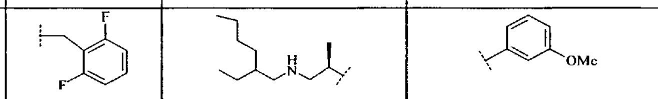
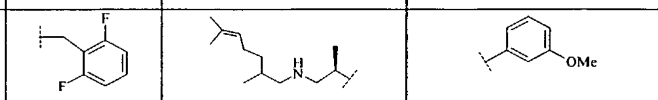
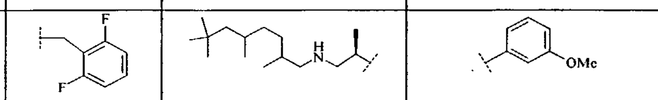
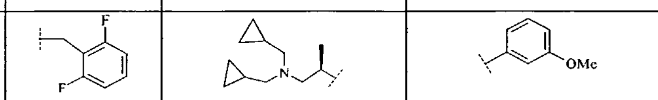
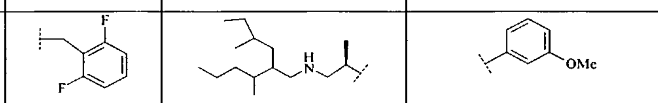
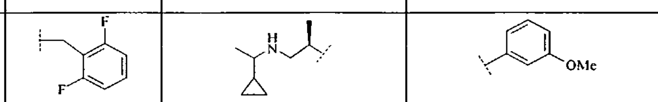
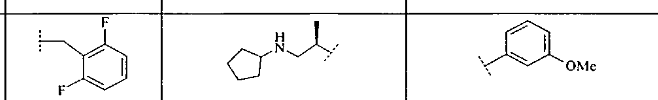
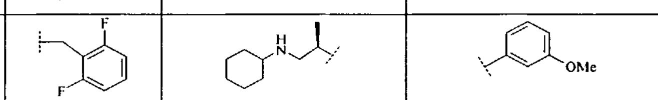
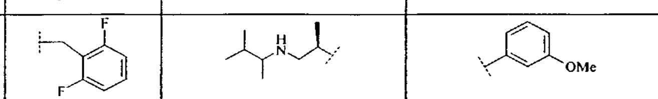
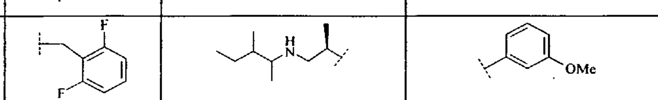
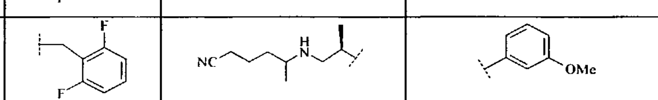
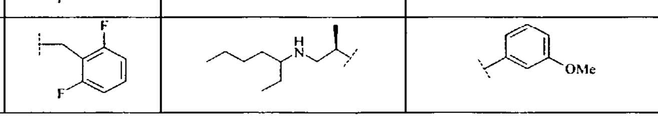
9-449	Me				530.57	531.2
9-450	Me				530.57	531.2
9-451	Me				530.57	531.2
9-452	Me				533.61	534.3
9-453	Me				533.61	534.3
9-454	Me				533.61	534.2
9-455	Me				535.58	536.2
9-456	Me				547.64	548.3
9-457	Me				548.63	549.3
9-458	Me				549.57	550.2
9-459	Me				535.58	536.2
9-460	Me				547.59	548.3
9-461	Me				556.00	556.2
9-462	Me				556.00	556.2
9-463	Me				556.00	556.2
9-464	Me				557.99	558.2

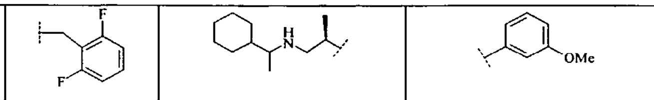
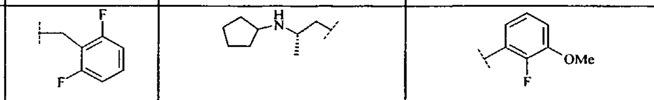
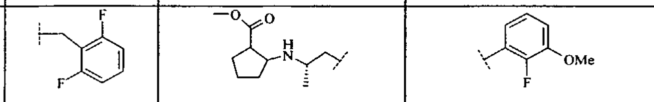
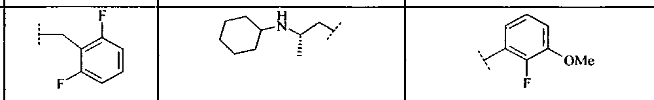
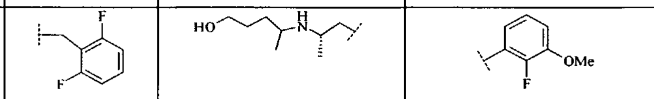
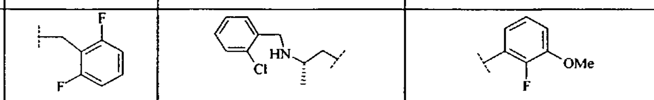
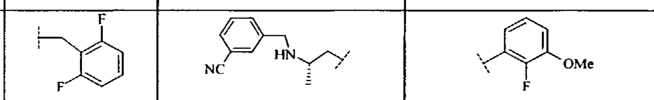
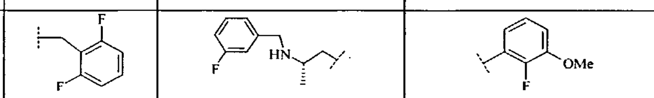
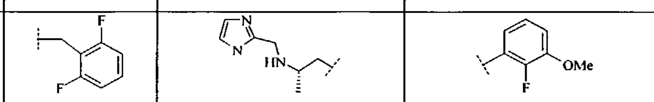
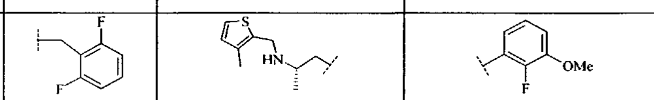
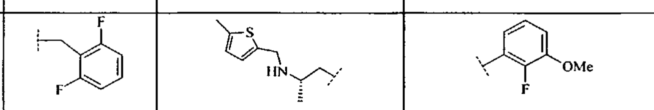
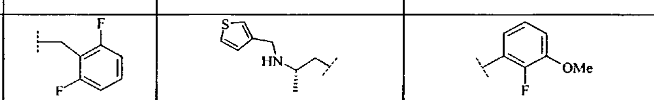
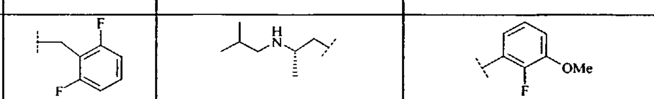
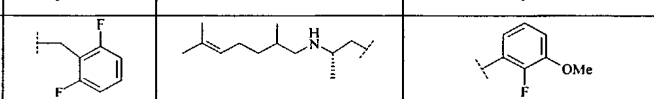
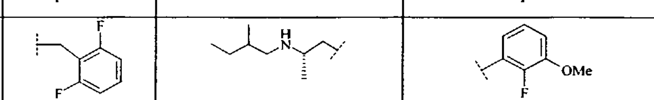
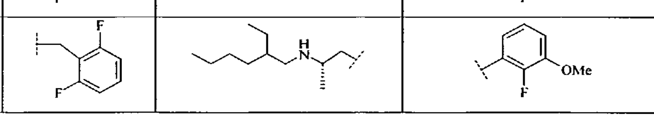
9-465	Me				557.99	558.2
9-466	Me				573.55	574.2
9-467	Me				544.59	545.2
9-468	Me				558.62	559.2
9-469	Me				495.52	496.2
9-470	Me				538.56	539
9-471	Me				495.52	496.2
9-472	Me				519.58	520.2
9-473	Me				519.58	520.2
9-474	Me				519.58	520.2
9-475	Me				521.56	535.2
9-476	Me				533.61	534.2
9-477	Me				535.58	536.2
9-478	Me				549.61	550.2
9-479	Me				551.65	552.2
9-480	Me				555.62	556.3

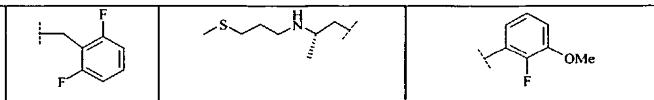
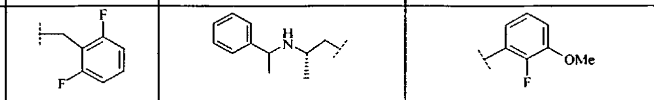
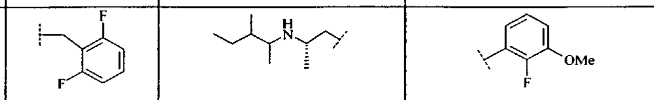
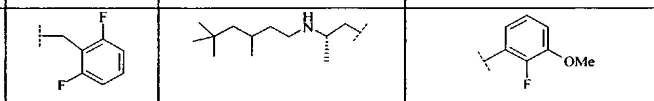
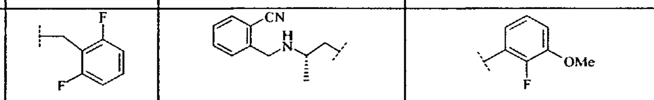
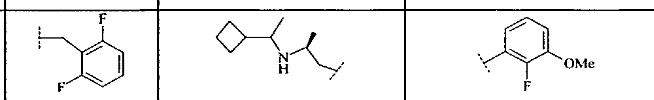
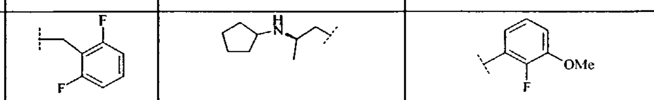
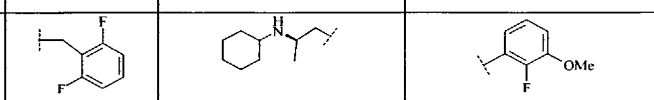
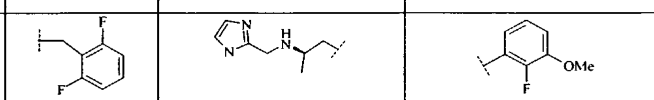
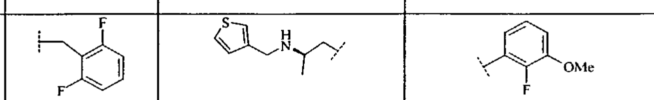
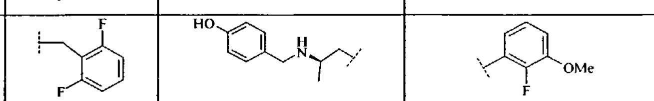
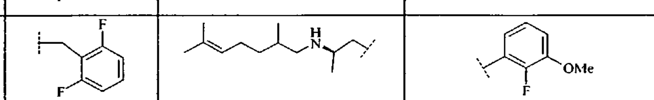
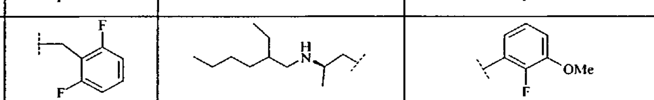
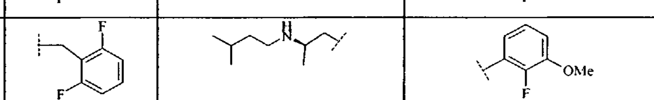
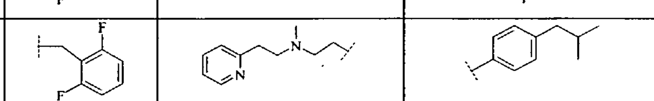
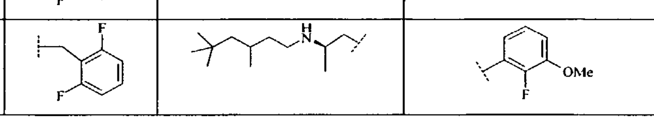
9-481	Me				552.59	553
9-482	Me				537.57	538.2
9-483	Me				539.55	540.2
9-484	Me				539.55	540.2
9-485	Me				541.54	542.2
9-486	Me				541.54	542.2
9-487	Me				541.54	542.2
9-488	Me				548.56	549.2
9-489	Me				548.56	549.3
9-490	Me				551.60	552.3
9-491	Me				551.60	552.2
9-492	Me				553.57	554.2
9-493	Me				553.57	554.2
9-494	Me				553.57	554.2
9-495	Me				565.58	566.2
9-496	Me				565.63	566.3

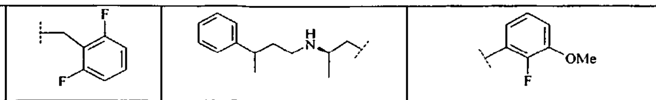
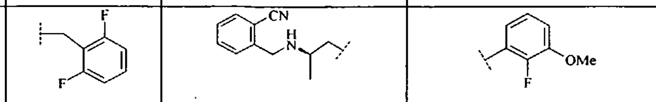
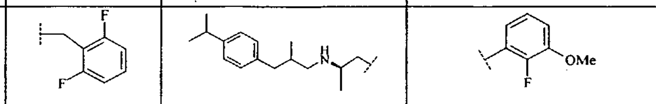
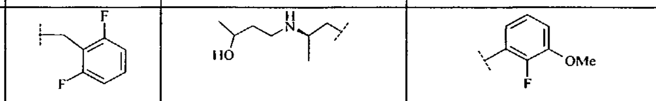
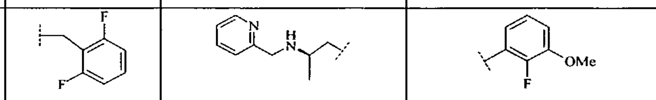
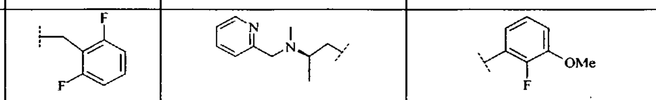
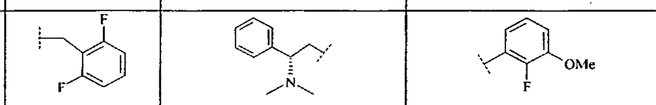
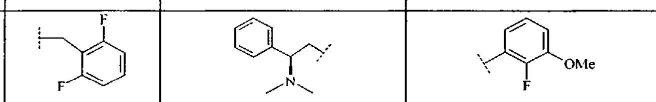
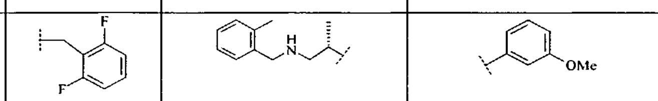
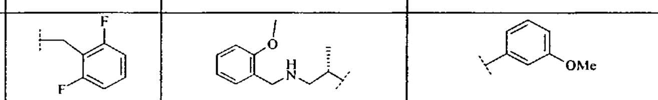
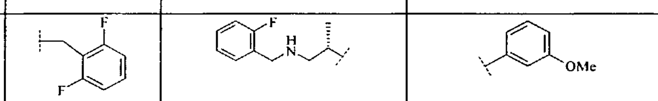
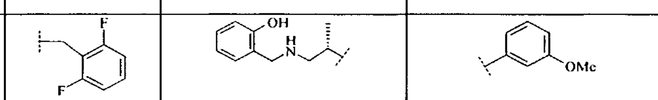
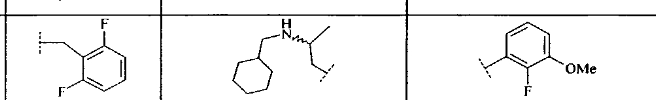
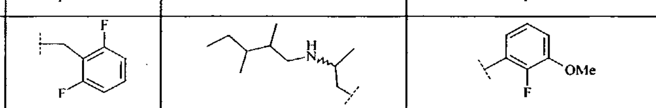
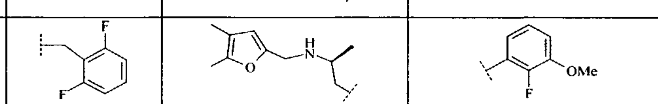
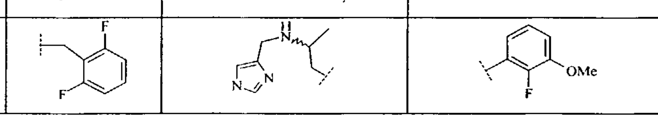
9-497	Me				565.63	566.3
9-498	Me				566.62	566.2
9-499	Me				567.56	567.3
9-500	Me				567.60	568.2
9-501	Me				569.64	568.2
9-502	Me				573.61	570.2
9-503	Me				573.99	574.2
9-504	Me				573.99	574.2
9-505	Me				573.99	574.2
9-506	Me				575.98	574.2
9-507	Me				575.98	576.2
9-508	Me				591.54	592.2
9-509	Me				562.58	563.2
9-510	Me				513.51	514.2
9-511	Me				513.51	514.2
9-512	Me				524.54	525.2

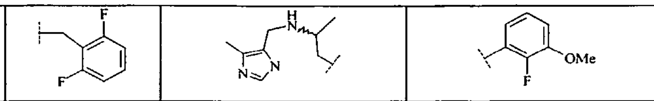
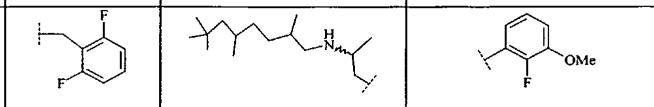
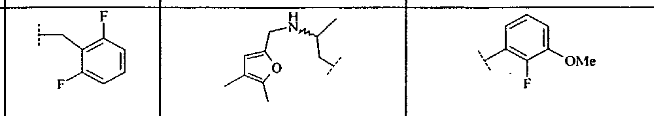
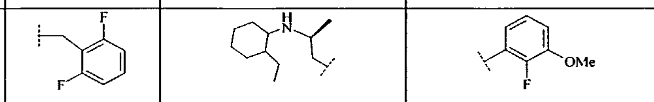
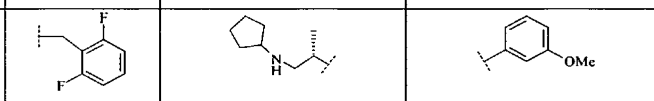
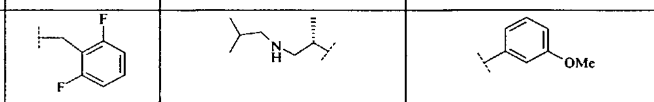
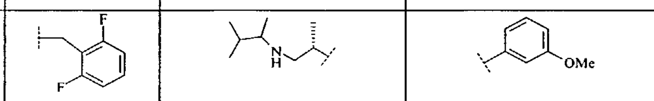
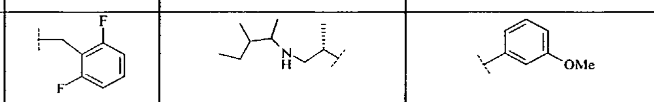
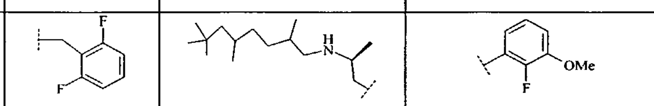
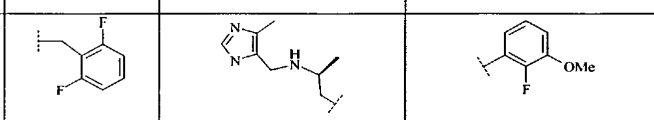
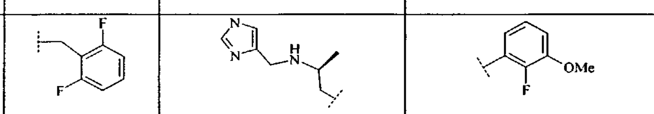
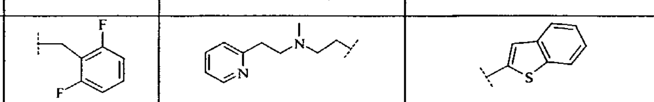
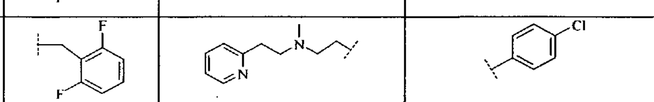
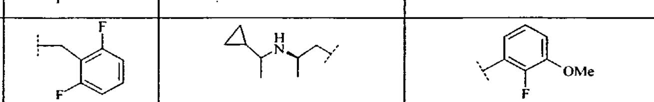
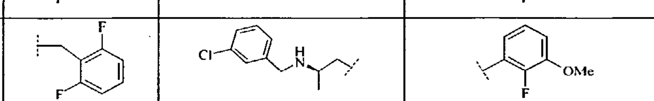
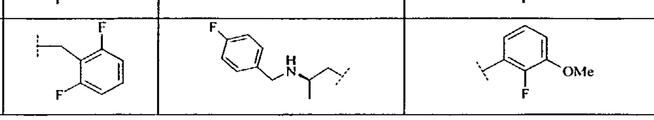
9-513	Me				547.64	548.3
9-514	Me				557.99	558.2
9-515	Me				525.63	526.3
9-516	Me				511.60	512.3
9-517	Me				523.55	524
9-518	Me				521.53	522
9-519	Me				555.63	556
9-520	Me			H	499.55	400 (MH-BOC)+
9-521	Me			H	399.43	400
9-522	Me			H	397.42	398
9-523	Me			Br	478.33	478/480
9-524	Me			Br	476.31	476/478
9-525	Me				505.56	506.3
9-526	Me				519.58	520.3
9-527	Me				505.56	506.2
9-528	Me				519.58	520.2

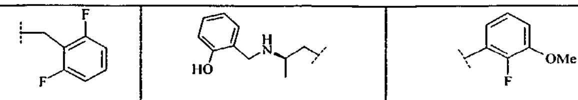
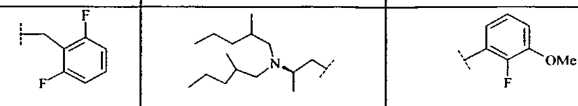
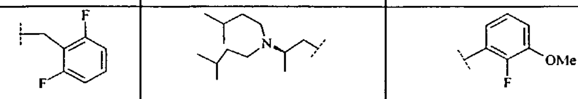
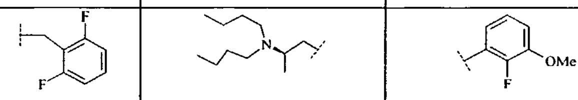
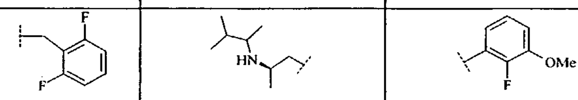
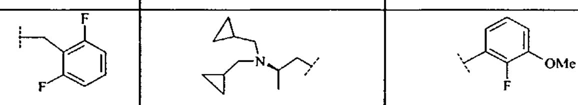
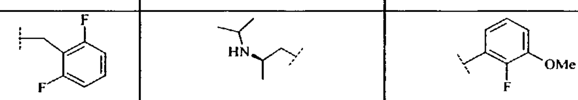
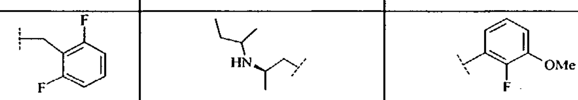
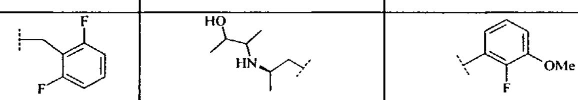
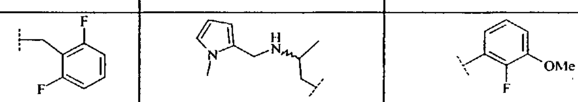
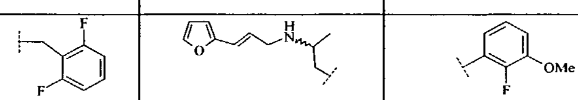
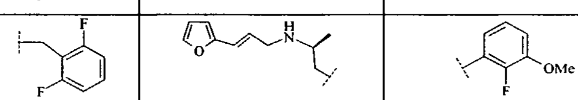
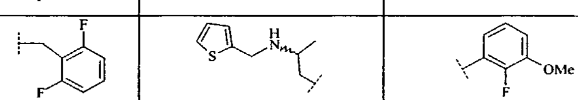
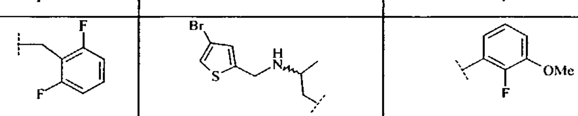
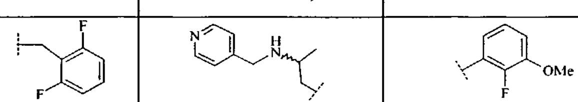
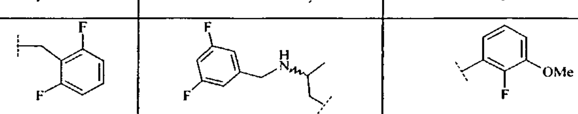
9-529	Me			471.54	472.2
9-530	Me			485.57	486.3
9-531	Me			499.59	500.3
9-532	Me			521.60	522.2
9-533	Me			527.65	528.3
9-534	Me			539.66	540.3
9-535	Me			583.75	584.4
9-536	Me			523.62	524.3
9-537	Me			555.70	556.3
9-538	Me			483.55	484.2
9-539	Me			483.55	484.2
9-540	Me			497.58	498.3
9-541	Me			485.57	486.3
9-542	Me			499.59	500.3
9-543	Me			510.58	511.2
9-544	Me			513.62	514.3

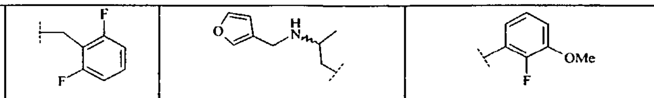
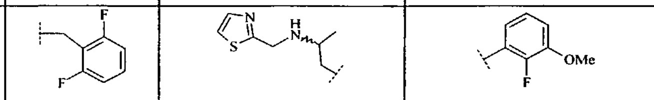
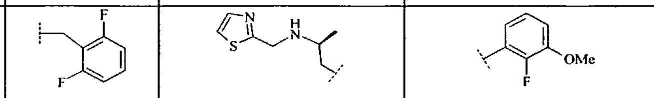
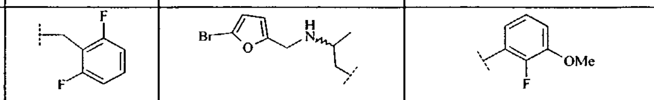
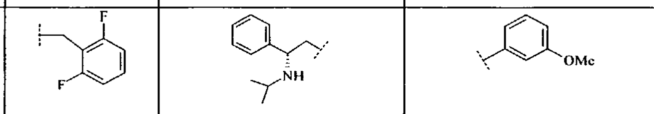
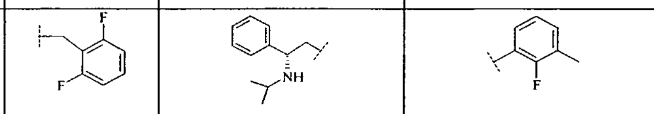
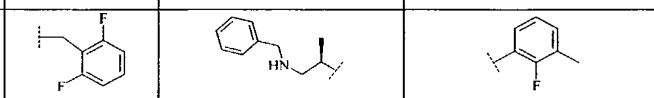
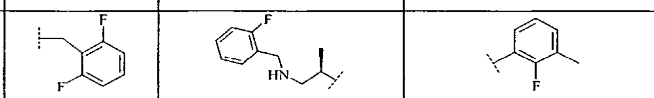
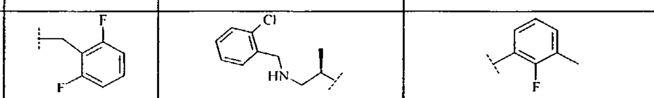
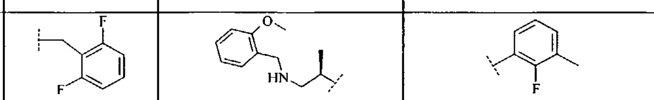
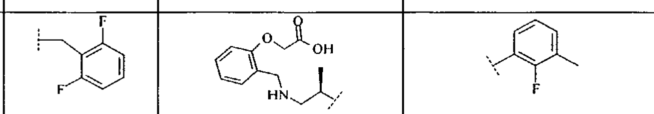
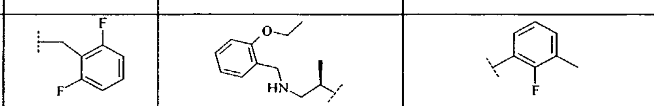
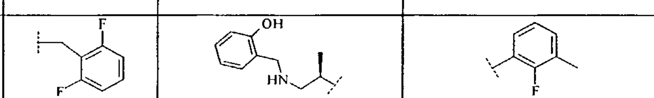
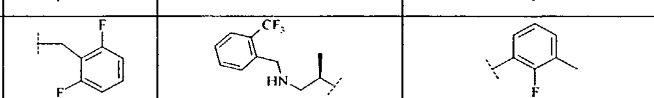
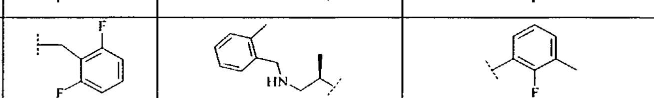
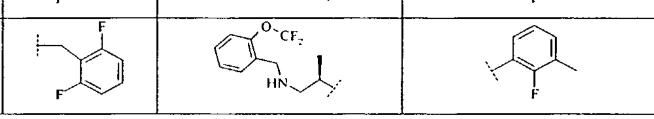
9-545	Me				525.63	526.3
9-546	Me				501.54	502.2
9-547	Me				559.58	560.2
9-548	Me				515.57	516.2
9-549	Me				519.56	520.2
9-550	Me				557.99	558.2
9-551	Me				548.56	549.2
9-552	Me				541.54	542.2
9-553	Me				513.51	514.2
9-554	Me				543.60	544.2
9-555	Me				543.60	544.2
9-556	Me				529.58	530.1
9-557	Me				489.53	490.2
9-558	Me				557.65	558.2
9-559	Me				503.56	504.2
9-560	Me				545.64	546.2

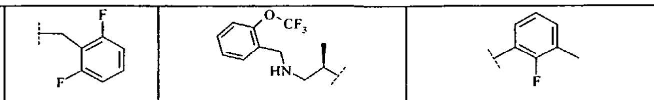
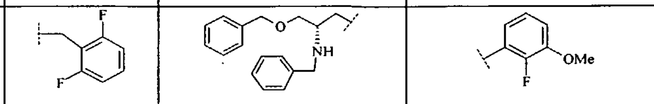
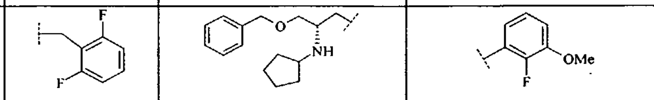
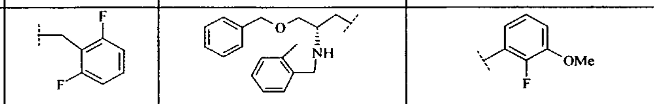
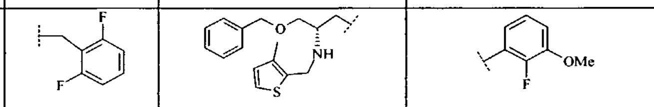
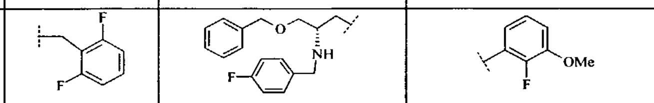
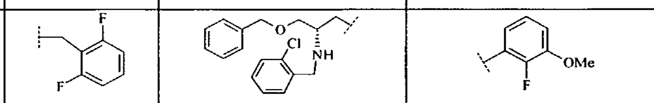
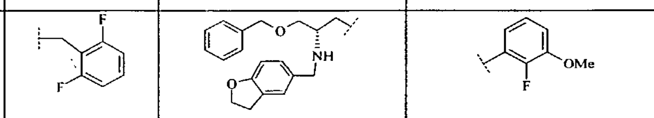
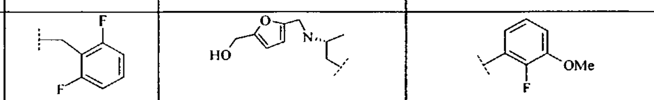
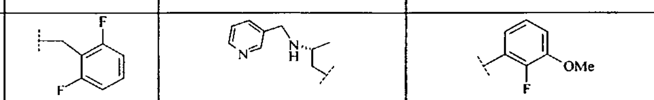
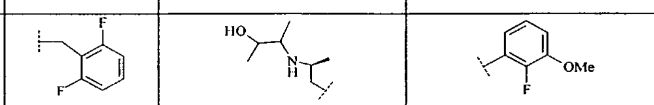
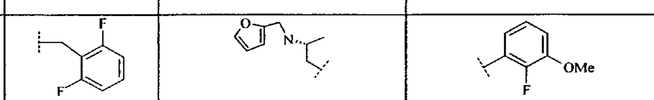
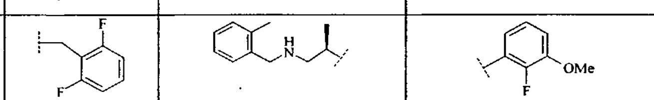
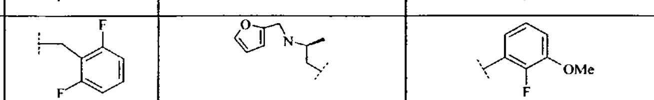
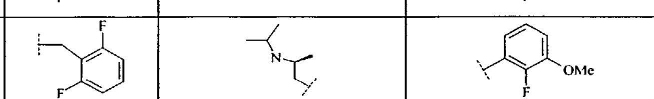
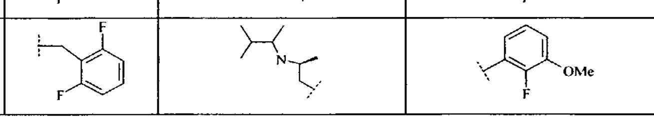
9-561	Me				521.60	522.2
9-562	Me				537.57	538.2
9-563	Me				517.58	518.2
9-564	Me				559.66	560.2
9-565	Me				548.56	549.2
9-566	Me				515.57	516.2
9-567	Me				501.54	502.2
9-568	Me				515.57	516.2
9-569	Me				513.51	514.2
9-570	Me				529.58	530.2
9-571	Me				539.55	540.2
9-572	Me				557.65	558.3
9-573	Me				545.64	546.3
9-574	Me				503.56	504.3
9-575	Me				546.65	547.3
9-576	Me				559.66	560.3

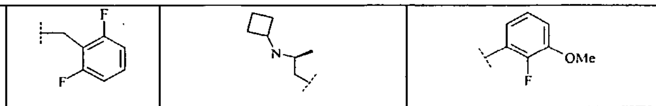
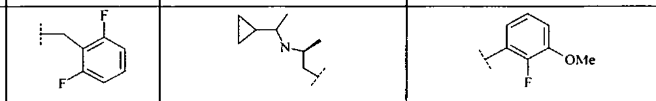
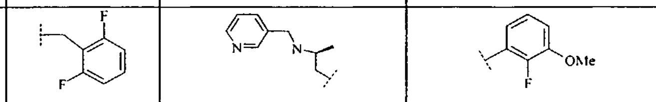
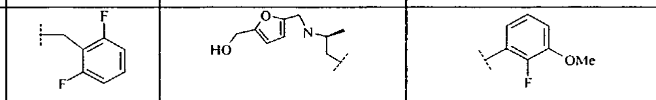
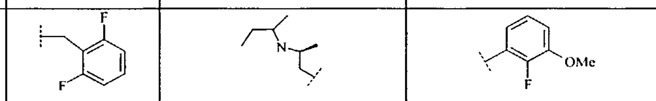
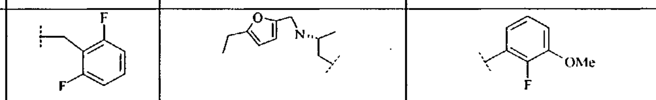
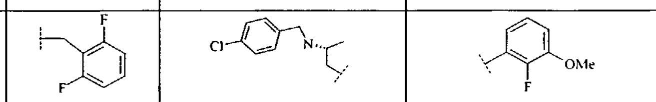
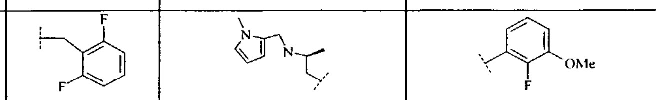
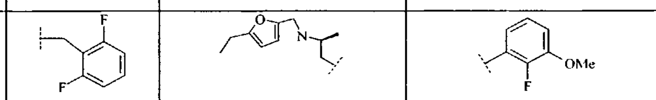
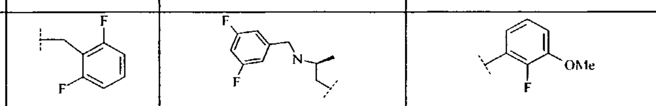
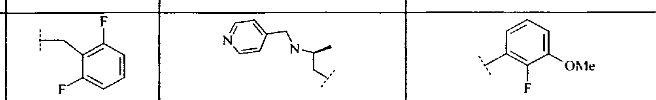
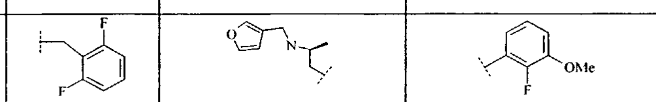
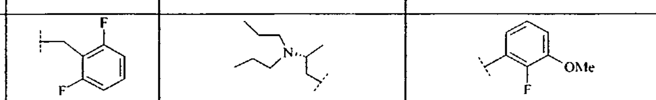
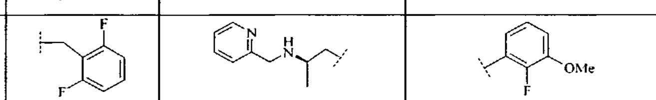
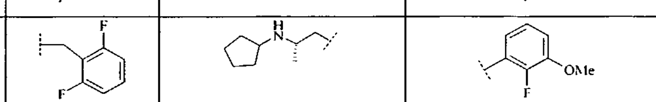
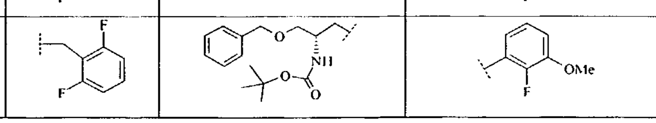
9-577	Me				565.63	566.3
9-578	Me				548.56	549.2
9-579	Me				607.71	608.4
9-580	Me				505.53	506.2
9-581	Me				524.54	525.2
9-582	Me				538.56	539.2
9-583	Me				523.55	524.2
9-584	Me				523.55	524.2
9-585	Me				519.58	520.2
9-586	Me				535.58	536.2
9-587	Me				523.55	524.2
9-588	Me				521.56	522.2
9-589	Me				529.6	530.2
9-590	Me				531.61	532.3
9-591	Me				541.56	542.3
9-592	Me				513.51	514.2

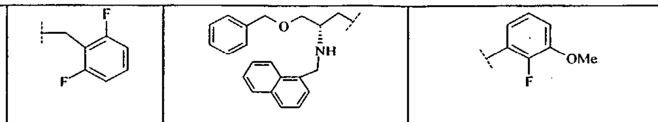
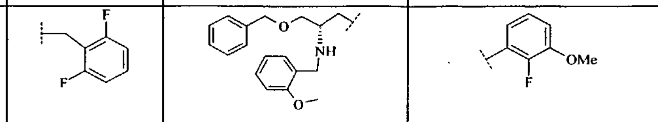
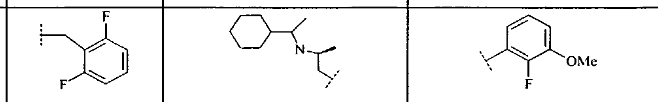
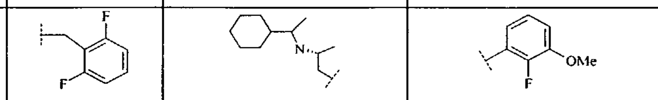
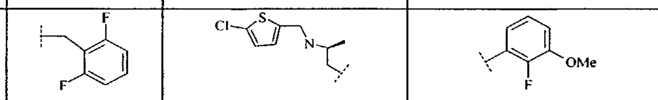
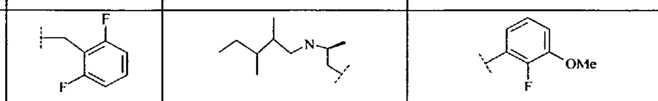
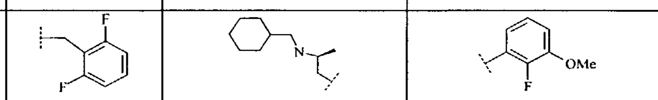
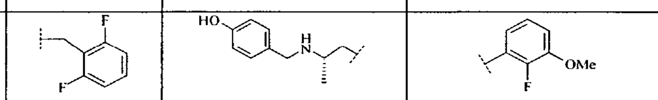
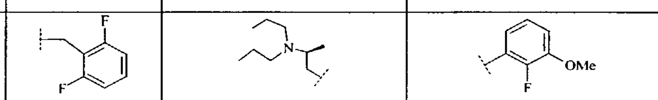
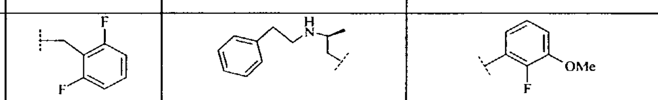
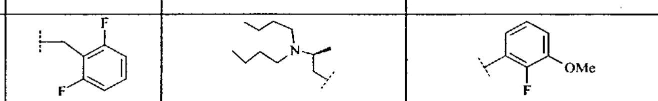
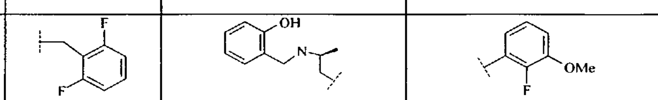
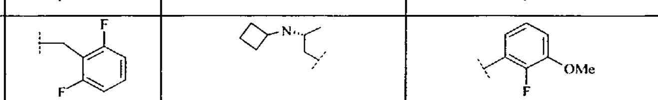
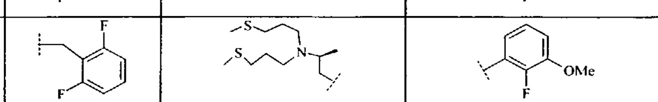
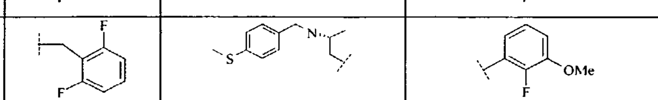
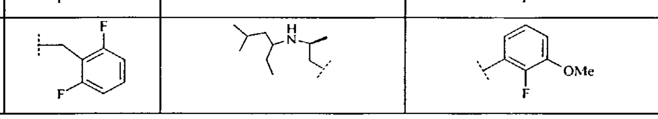
9-593	Me				527.54	528.2
9-594	Me				601.74	602.4
9-595	Me				541.56	542.2
9-596	Me				543.62	542.2
9-597	Me				483.55	484.2
9-598	Me				471.54	472.1
9-599	Me				485.57	486.3
9-600	Me				499.59	500.3
9-601	Me				601.74	602.4
9-602	Me				527.54	528.2
9-603	Me				513.51	514.2
9-604	Me				546.63	547
9-605	Me				524.99	525
9-606	Me				501.54	502.2
9-607	Me				557.99	558.2
9-608	Me				541.54	542.2

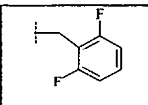
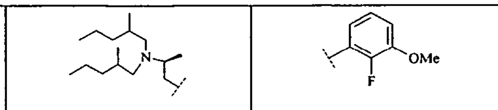
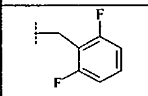
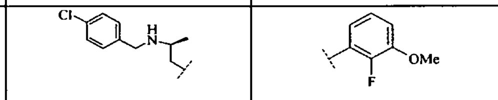
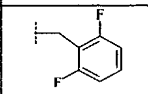
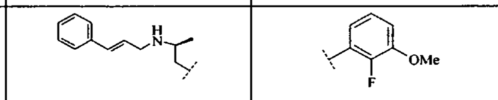
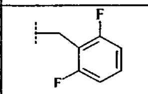
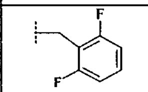
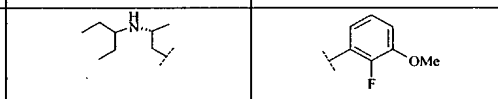
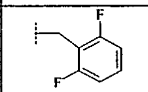
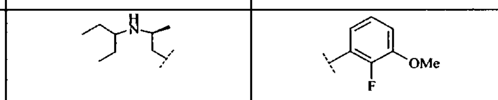
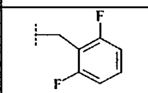
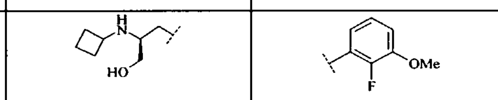
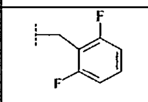
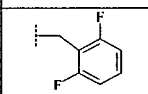
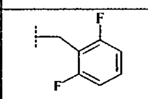
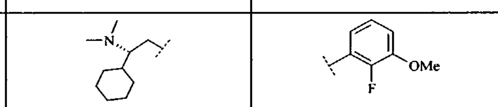
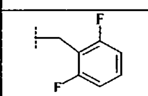
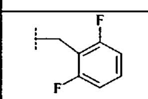
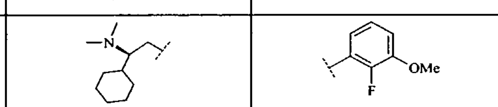
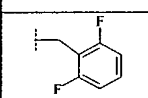
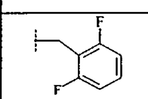
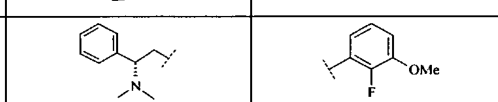
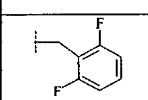
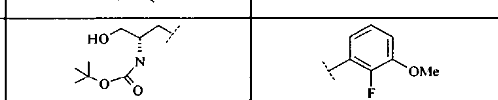
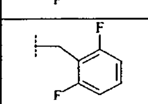
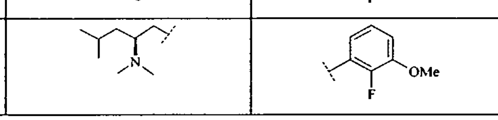
9-609	Me				539.55	540.3
9-610	Me				601.74	602.4
9-611	Me				573.69	574.3
9-612	Me				545.64	546.3
9-613	Me				503.56	504.2
9-614	Me				541.61	542.3
9-615	Me				475.50	476.2
9-616	Me				489.53	490.3
9-617	Me				505.53	506.30
9-618	Me				526.55	527.2
9-619	Me				539.55	540.2
9-620	Me				539.55	540.2
9-621	Me				529.58	530.2
9-622	Me				608.47	608.1
9-623	Me				524.54	525.2
9-624	Me				559.53	560.2

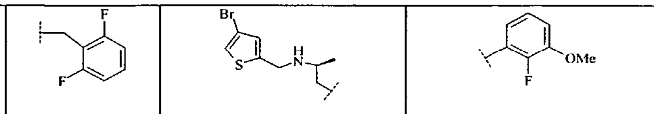
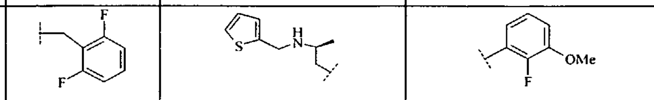
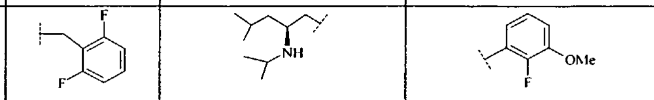
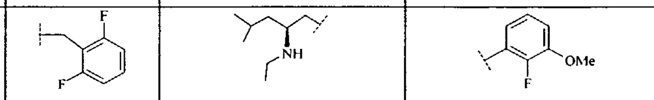
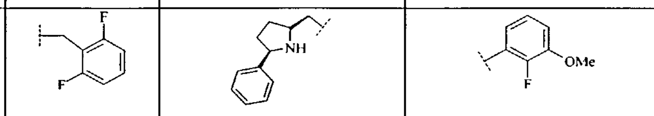
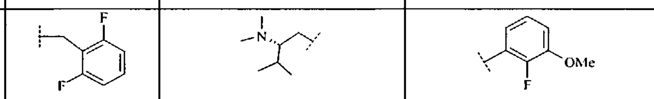
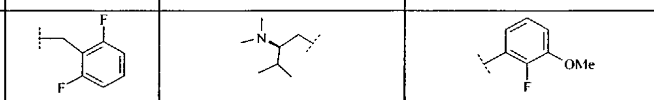
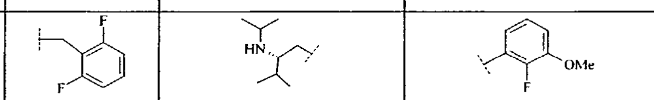
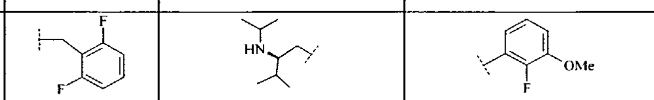
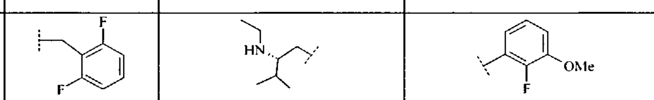
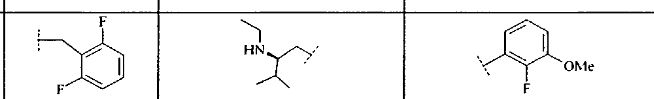
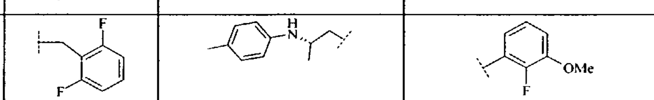
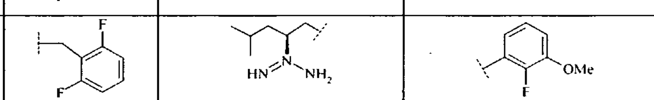
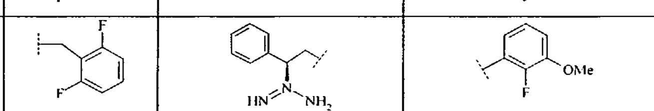
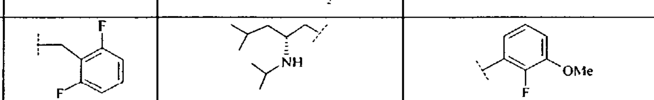
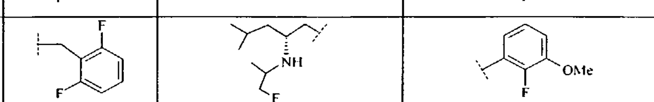
9-625	Me				513.51	514.2
9-626	Me				530.56	531.2
9-627	Me				530.56	531.2
9-628	Me				592.40	594.1
9-629	Me				519.58	520.2
9-630	Me				521.58	522.2
9-631	Me				507.55	508.3
9-632	Me				525.54	526.2
9-633	Me				541.99	542.2
9-634	Me				537.57	538.3
9-635	Me				581.58	582.2
9-636	Me				551.60	552.3
9-637	Me				523.55	524.2
9-638	Me				575.55	576.2
9-639	Me				521.58	522.2
9-640	Me				573.55	574.2

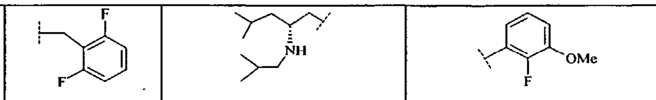
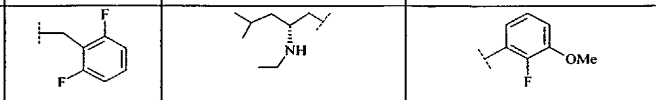
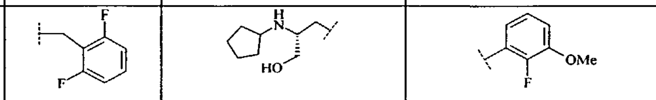
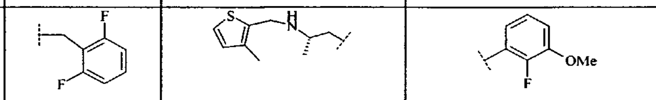
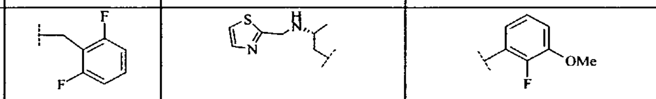
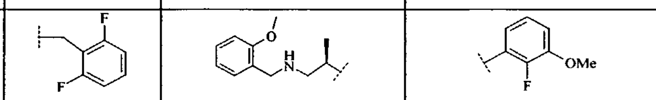
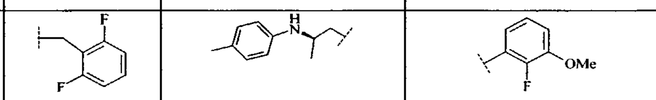
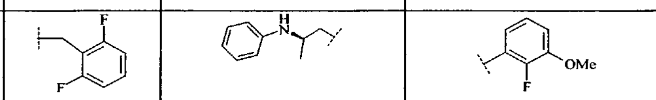
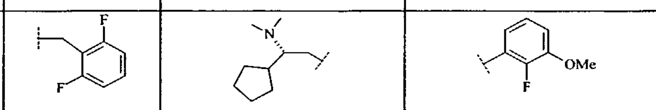
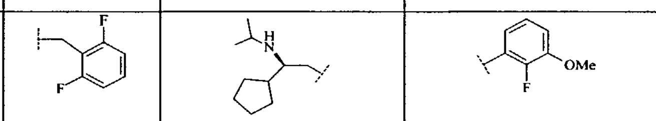
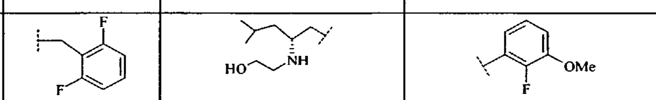
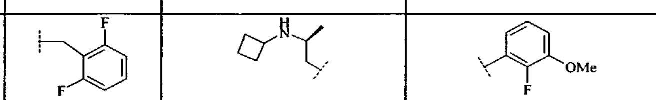
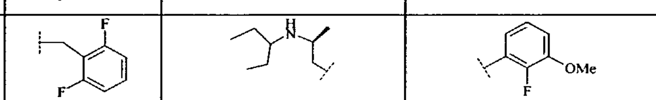
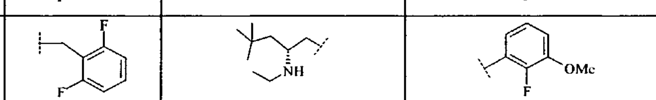
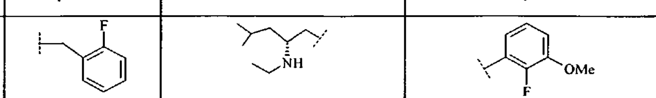
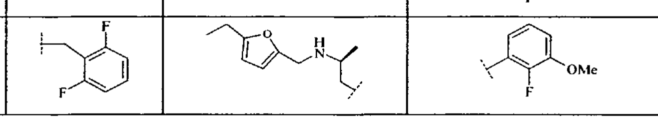
9-641	Me				591.54	592.2
9-642	Me				629.67	630
9-643	Me				607.66	608
9-644	Me				643.70	644
9-645	Me				649.73	650
9-646	Me				647.66	648
9-647	Me				664.12	664
9-648	Me				671.71	672
9-649	Me				543.53	544.2
9-650	Me				524.54	525.2
9-651	Me				505.53	506.2
9-652	Me				513.51	514.2
9-653	Me				537.57	538.3
9-654	Me				513.51	514.2
9-655	Me				475.50	476.2
9-656	Me				503.56	504.3

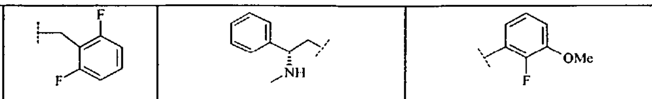
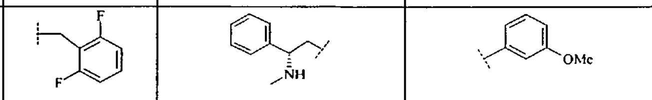
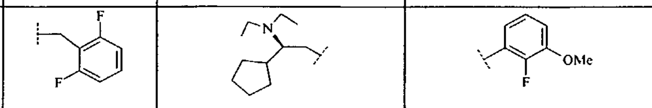
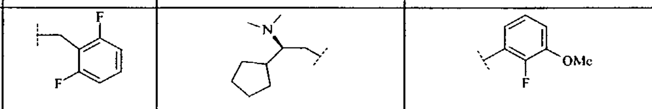
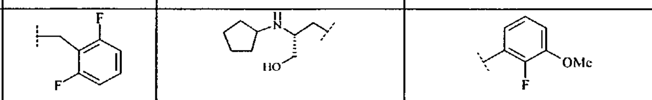
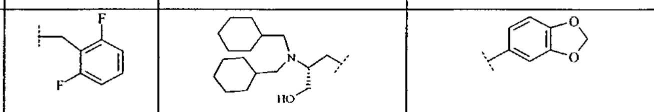
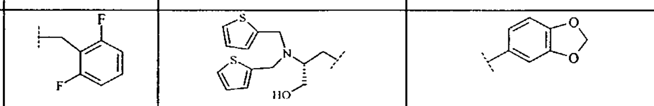
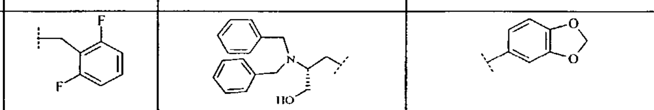
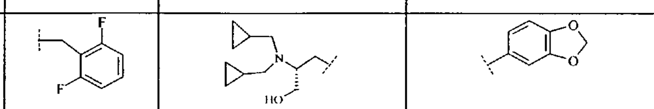
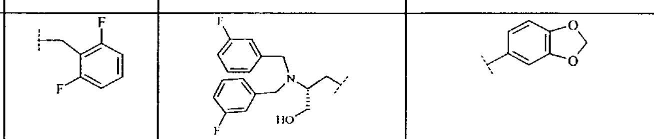
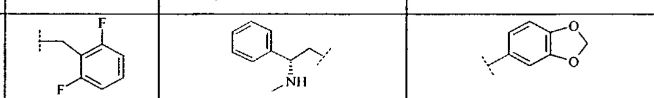
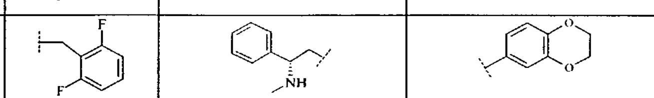
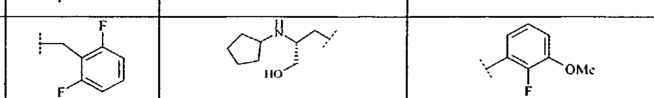
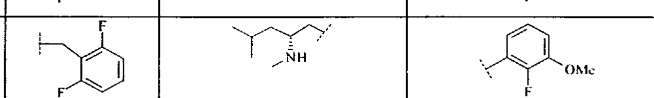
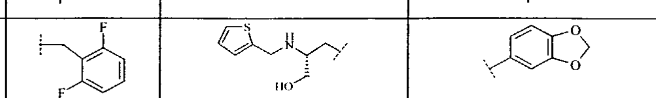
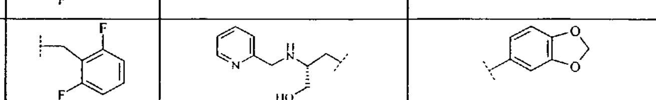
9-657	Me		487.51	488.3
9-658	Me		501.54	502.2
9-659	Me		524.54	525.2
9-660	Me		543.53	544.2
9-661	Me		489.53	490.3
9-662	Me		541.56	542.3
9-663	Me		557.99	558.2
9-664	Me		526.55	527.2
9-665	Me		541.56	542.3
9-666	Me		559.53	560.2
9-667	Me		524.54	525.2
9-668	Me		513.51	514.2
9-669	Me		517.58	518.2
9-670	Me		524.54	525.2
9-671	Me		501.54	502
9-672	Me		639.66	540

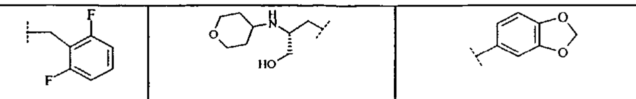
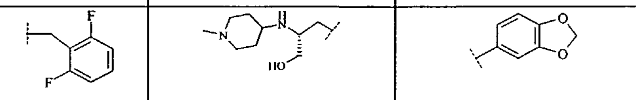
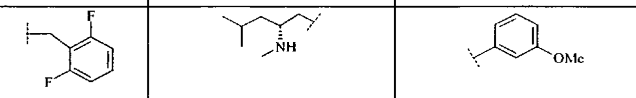
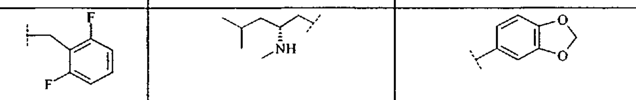
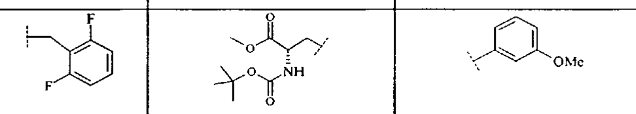
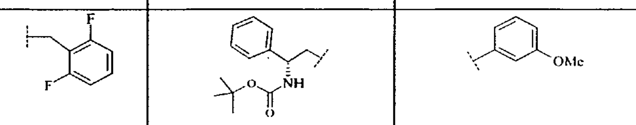
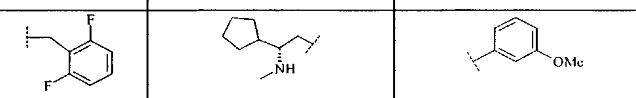
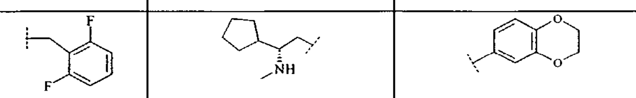
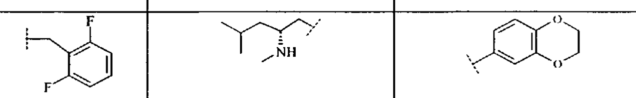
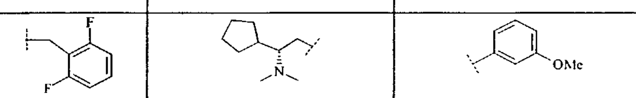
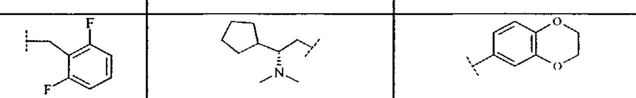
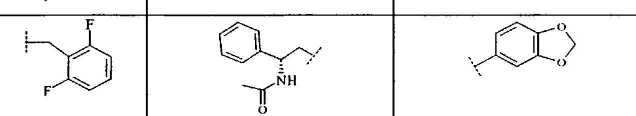
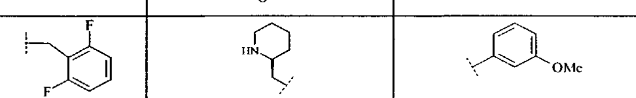
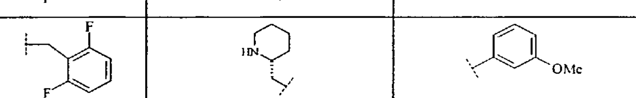
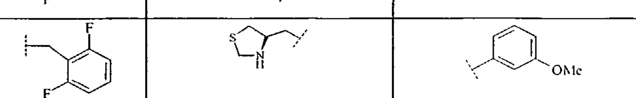
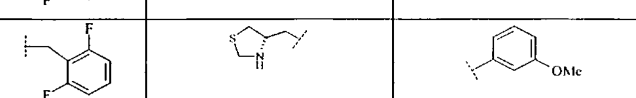
9-673	Me				679.73	680
9-674	Me				659.70	660
9-675	Me				543.62	544.3
9-676	Me				543.62	544.3
9-677	Me				564.02	564.2
9-678	Me				531.61	532.3
9-679	Me				529.6	530.2
9-680	Me				539.55	540.2
9-681	Me				517.58	518.3
9-682	Me				537.57	538.2
9-683	Me				545.64	544.3
9-684	Me				539.55	540.2
9-685	Me				487.51	488.2
9-686	Me				609.77	610.3
9-687	Me				569.64	570.2
9-688	Me				531.61	532.3

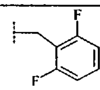
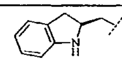
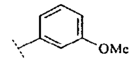
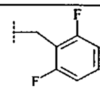
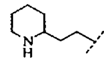
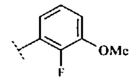
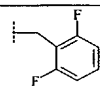
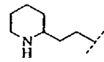
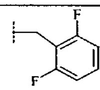
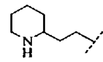
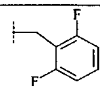
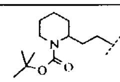
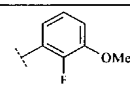
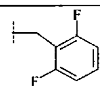
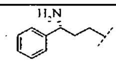
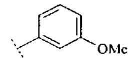
9-689	Me				601.74	602.4
9-690	Me				557.99	558.2
9-691	Me				549.59	550.2
9-692	Me				517.58	518.2
9-693	Me				503.56	504.3
9-694	Me				503.56	504.3
9-695	Me				503.51	504
9-696	Me				537.53	538.2
9-697	Me				551.60	552.3
9-698	Me				529.6	530.2
9-699	Me				543.62	544.3
9-700	Me				529.6	530.2
9-701	Me				543.62	544.3
9-702	Me				523.55	524.2
9-703	Me				549.54	450
9-704	Me				503.56	504.3

9-705	Me		608.47	610.1
9-706	Me		529.58	530.2
9-707	Me		517.58	518.2
9-708	Me		503.56	504.3
9-709	Me		535.56	536.2
9-710	Me		489.53	490.2
9-711	Me		489.53	490.2
9-712	Me		503.56	504.2
9-713	Me		503.56	504.2
9-714	Me		489.53	490.2
9-715	Me		489.53	490.2
9-716	Me		523.55	524.2
9-717	Me		517.54	518.2
9-718	Me		523.55	524
9-719	Me		517.58	518.3
9-720	Me		535.57	536.3

9-721	Me				531.61	532.3
9-722	Me				503.56	504.3
9-723	Me				517.54	518
9-724	Me				543.60	544
9-725	Me				530.56	531
9-726	Me				553.57	554
9-727	Me				523.55	524.2
9-728	Me				509.52	510.2
9-729	Me				515.57	516.3
9-730	Me				529.6	530.3
9-731	Me				519.56	520.2
9-732	Me				487.519	488
9-733	Me				503.562	504
9-734	Me				517.6	518.2
9-735	Me				485.6	486.2
9-736	Me				541.6	542

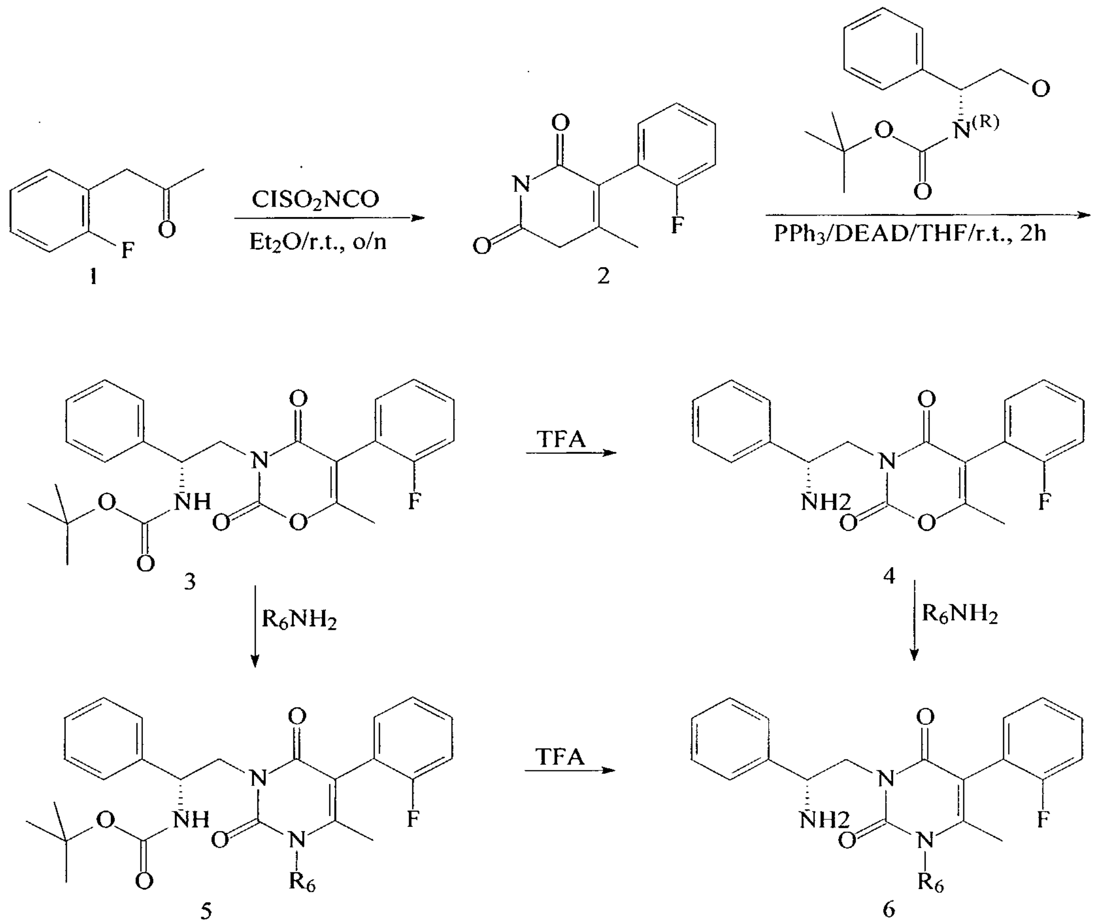
9-737	Me				509.5	510.2
9-738	Me				491.5	492.2
9-739	Me				543.6	544.3
9-740	Me				515.6	516.3
9-741	Me				513.5	514
9-742	Me				637.8	638
9-743	Me				637.7	638
9-744	Me				625.7	626
9-745	Me				553.6	554
9-746	Me				661.6	662
9-747	Me				505.5	506.2
9-748	Me				519.5	520.2
9-749	Me				517.5	518
9-750	Me				489.5	490.2
9-751	Me				541.6	542
9-752	Me				536.5	537

9-753	Me				529.5	530
9-754	Me				542.6	543
9-755	Me				471.5	472.2
9-756	Me				485.5	486.2
9-757	Me				559.6	460.2
9-758	Me				527.6	428.2
9-759	Me				483.6	484.2
9-760	Me				511.6	512.2
9-761	Me				49.6	500.2
9-762	Me				497.6	498.2
9-763	Me				525.6	526.2
9-764	Me				533.5	534.2
9-765	Me				455.5	456.2
9-766	Me				455.5	456.2
9-767	Me				459.5	460.1
9-768	Me				459.5	459

9-769	Me				489.5	489
9-770	Me				487.5	488
9-771	Me			Br	442.3	442
9-772	Me			H	363.4	364
9-773	Me				587.6	588
9-774	Me				491.5	491

EXAMPLE 10

SYNTHESIS OF REPRESENTATIVE COMPOUNDS



Step A 6-Methyl-5-(2-fluorophenyl)-oxaz-2,4-dione

To a stirred solution of 2'-fluorophenylacetone **1** (7.6 g, 50 mmol) in ether (50 mL) was added dropwise chlorosulfonylisocyanate (CSI, 16.2 g, 115 mmol) at room temperature. The yellow solution was stirred overnight, poured into ice (100 g) and basified with sodium carbonate. The product was extracted with ethyl acetate (2x200 mL) and the extract was washed with water and brine, dried over magnesium sulfate and concentrated in vacuo to give a yellow residue (9.5 g, proton NMR, about 70% product). The crude product was crystallized from ether-hexanes to give compound **2** as a yellow solid (3.6 g, 33% yield); ^{1}H NMR ($CDCl_3$): 2.14 (s, 3H), 7.16 (t, J = 9.0Hz, 1H), 7.24 (m, 2H), 7.41 (m, 1H), 9.20 (brs, 1H).

Step B <u>6-Methyl-5-(2-fluorophenyl)-3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]oxaz-2,4-dione</u>

DEAD (348 mg, 1.2 mmol) was added into a solution of oxazine **2** (221 mg, 1.0 mmol), triphenylphosphine (314 mg, 1.2 mmol) and N-Boc-(R)-phenylglysinol (249 mg, 1.05 mmol) in dry THF (5 mL). The mixture was stirred at room temperature for 2 hours, concentrated, and purified by chromatography on silica gel with 1:3 ethyl acetate/hexanes to give the product **3** (380 mg, 87%) as a white solid; ^{1}H NMR ($CDCl_3$): 1.39 (s, 9H), 2.14 (s, 3H), 4.02 (m, 1H), 4.28 (m, 1H), 5.21 (brs, 1H), 5.30 (m, 1H), 7.38 (m, 9H); MS (341, MH^+-BuOCO).

Step C <u>6-Methyl-5-(2-fluorophenyl)-3-[2(R)-amino-2-phenylethyl]oxaz-2,4-dione trifluoroacetic acid salt</u>

6-Methyl-5-(2-fluorophenyl)-3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]oxaz-2,4-dione **3** (30 mg) was treated with trifluoroacetic acid (1 mL) at room temperature for 30 minutes. Concentration in vacuo gave the title compound **4** as a colorless oil in quantitative yield; ^{1}H NMR ($CDCl_3$): 2.05 & 2.08 (s, 3H), 4.10 (m, 1H), 4.45 (m, 1H), 4.62 (m, 1H), 7.15 (m, 3H), 7.40 (m, 6H), 8.20 (brs, 3H); MS: 341 (MH^+).

Step D <u>6-Methyl-5-(2-fluorophenyl)-3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]-1-(2-methoxybenzyl)uracil</u>

A mixture of 6-methyl-5-(2-fluorophenyl)-3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]oxaz-2,4-dione **3** (29 mg) and 2-methoxybenzylamine (0.15 mL) was heated in a sealed reacti-vial at 100°C for 1 hour. Chromatography on silica gel with 1:2 ethyl acetate-hexanes gave compound **5** as a colorless oil; ^{1}H NMR ($CDCl_3$): 1.40 (s, 9H), 2.04 (s, 3H), 3.87 (s, 3H), 4.18 (m, 1H), 4.44 (m, 1H), 5.22 (m, 2H), 5.65 (brs, 1H), 5.78 (m, 1H), 6.85-7.42 (m, 13H); MS: 460 (MH^+-BuOCO).

The following protected intermediates were made using the same procedure but substituting different amines for 2-methoxybenzylamine. Acetic acid may be used to catalyze the reaction.

6-Methyl-5-(2-fluorophenyl)-3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]-1-(2,6-difluorobenzyl)uracil

^{1}H NMR ($CDCl_3$): 1.39 (s, 9H), 2.18 (s, 3H), 4.10 (m, 1H), 4.38 (m, 1H), 4.90-5.80 (m, 4H), 6.92 (m, 2H), 7.10-7.42 (m, 10H); MS: 466 (MH^+-BuOCO).

6-Methyl-5-(2-fluorophenyl)-3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]-1-(2-chlorobenzyl)uracil

^{1}H NMR ($CDCl_3$): 1.40 (s, 9H), 2.02 (s, 3H), 4.15 (m, 1H), 4.50 (m, 1H), 5.35 (m, 3H), 5.62 (m, 1H), 6.95 (m, 13H); MS: 464 (MH^+-BuOCO).

6-Methyl-5-(2-fluorophenyl)-3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]-1-(2-methylbenzyl)uracil

^{1}H NMR ($CDCl_3$): 1.40 (s, 9H), 2.02 (s, 3H), 2.37 (s, 3H), 4.15 (m, 1H), 4.42 (m, 1H), 5.72 (m, 1H), 6.80-7.42 (m, 13H); MS: 444 (MH^+-BuOCO).

Step E <u>6-Methyl-5-(2-fluorophenyl)-3-[2(R)-amino-2-phenylethyl]-1-(2-methoxybenzyl)uracil trifluoroacetic acid salt</u>

6-Methyl-5-(2-fluorophenyl)-3-[2(R)-tert-butoxycarbonylamino-2-phenylethyl]-1-(2-methoxybenzyl)uracil **5** (20 mg) was treated with trifluoroacetic acid (1 mL) at room temperature for 30 minutes. Concentration in vacuo gave the product **6** as a colorless oil in quantitative yield; ^{1}H NMR ($CDCl_3$): 2.04 (s, 3H), 3.82 & 3.85 (s, 3H), 4.20 (m, 1H), 4.62 (m, 2H), 5.10 (m, 2H), 6.82-7.40 (m, 13H), 8.05 (brs, 3H); MS: 460 (MH^+).

The following products were also prepared using the same procedure.

6-Methyl-5-(2-fluorophenyl)-3-[2(R)-amino-2-phenylethyl]-1-(2-chlorobenzyl)uracil trifluoroacetic acid salt

^{1}H NMR ($CDCl_3$): 2.01 (s, 3H), 4.20 (m, 1H), 4.70 (m, 2H), 5.25 (m, 2H), 6.90-7.45 (m, 13H), 8.20 (brs, 3H); MS: 464 (MH^+).

6-Methyl-5-(2-fluorophenyl)-3-[2(R)-amino-2-phenylethyl]-1-(2-methylbenzyl)uracil trifluoroacetic acid salt

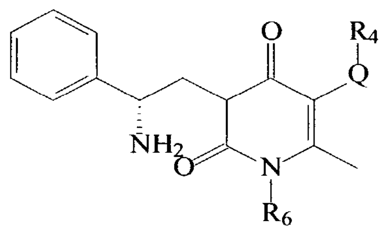
^{1}H NMR ($CDCl_3$):2.00 (s, 3H), 2.27 & 2.34 (s, 3H), 4.15 (m, 4H), 4.62 (m, 2H), 5.15 (m, 2H), 6.80-7.40 (m, 13H); MS: 444 (MH^+).

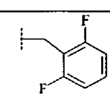
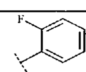
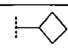
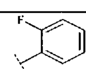
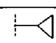
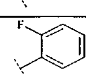
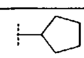
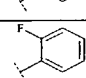
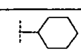
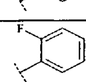
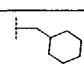
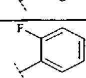
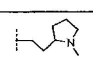
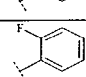
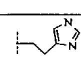
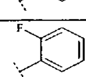
6-Methyl-5-(2-fluorophenyl)-3-[2(R)-amino-2-phenylethyl]-1-(2,6-difluorobenzyl)uracil trifluoroacetic acid salt

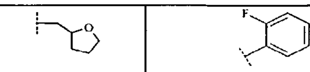
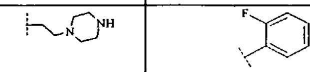
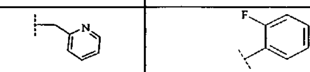
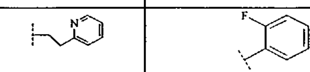
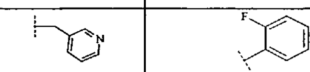
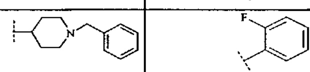
^{1}H NMR ($CDCl_3$): 2.14 (s, 3H), 4.18 (m, 1H), 4.62 (m, 2H), 5.20 (m, 2H), 5.62 (brs, 3H), 6.85-7.40 (m, 13H); MS: 466 (MH^+).

By the above procedure, the compounds of the following Table 10 were also prepared.

Table 10



Cpd. No.	R_6	-Q-R_4	MW (calc.)	(obs.)
10-1			465.5	466
10-2			393.5	394.2
10-3			379.4	363
10-4			407.5	323.3
10-5			421.5	405.4
10-6			435.5	436.2
10-7			450.6	451.3
10-8			433.5	417.3

10-9			423.5	407.2
10-10			435.5	419.2
10-11			451.5	452.3
10-12			436.5	323.3
10-13			466.6	450.3
10-14			430.5	414.4
10-15			444.5	428.4
10-16			430.5	414.4
10-17			430.5	414.4
10-18			512.6	513.3
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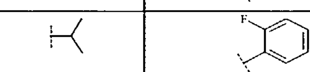
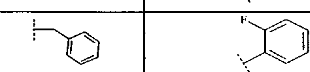
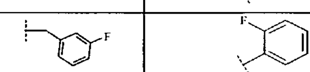
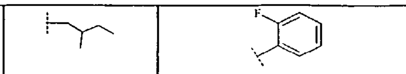
10-20			381.4	382.2
10-21			429.5	413.2
10-22			447.5	431.4
10-23			447.5	431.3
10-24			498.4	481.4
10-25			459.5	443.3
10-26			443.5	427.2
10-27			463.9	447.1
10-28			443.5	427.2
10-29			397.4	398.2
10-30			395.5	379.2

10-31			409.5	393.3
10-32			396.5	380.3
10-33			410.5	394.1
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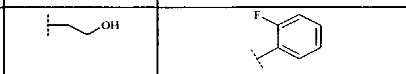
10-35			383.4	367.1
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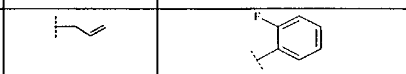
10-37			379.4	363.3
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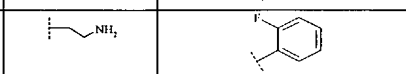
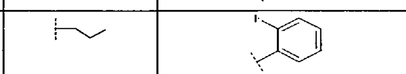
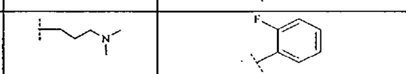
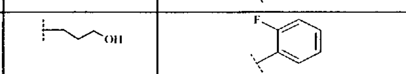
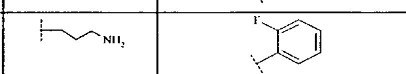
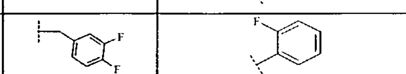
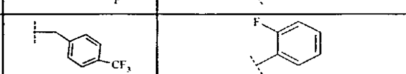
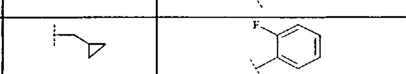
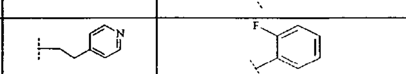
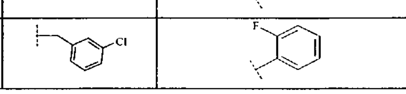
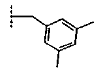
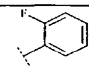
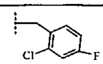
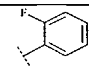
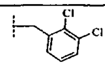
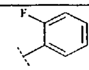
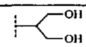
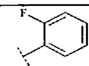
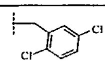
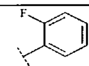
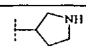
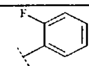
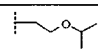
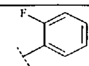
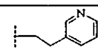
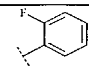
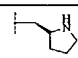
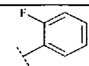
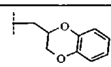
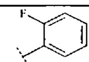
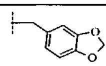
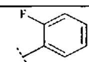
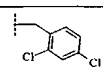
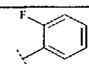
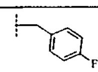
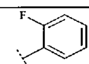
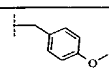
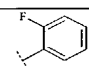
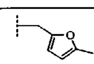
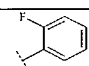
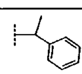
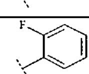
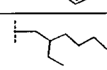
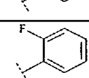
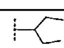
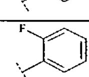
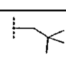
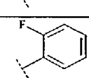
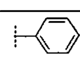
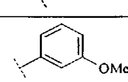
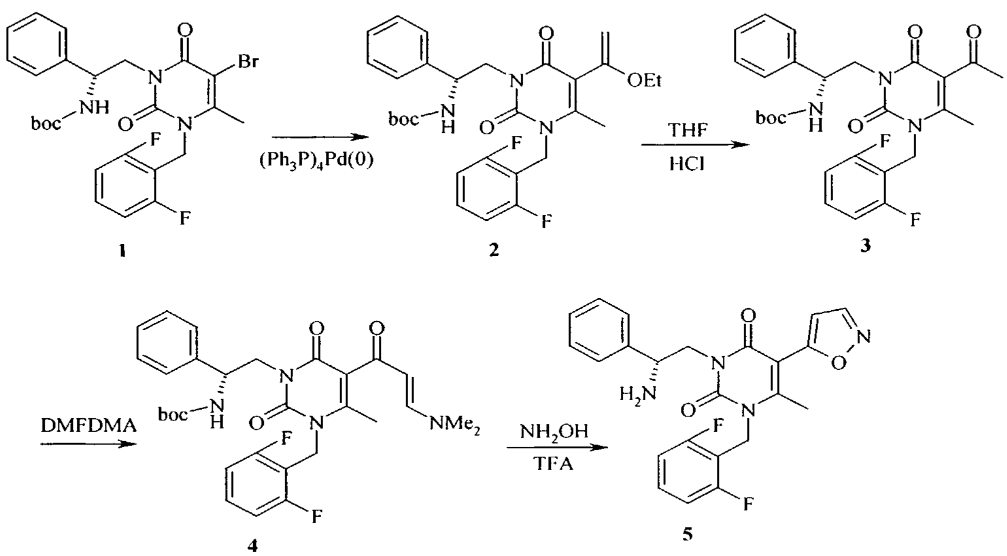
10-39			382.4	366.2
10-40			381.4	365.2
10-41			424.5	408.5
10-42			397.4	381.2
10-43			396.5	380.3
10-44			409.5	393.3
10-45			465.5	449.4
10-46			497.5	481.4
10-47			395.5	379.3
10-48			450.6	451.3
10-49			411.5	395.2
10-50			393.5	377.3
10-51			444.5	428.4
10-52			463.9	447.1

10-53			457.5	441.3
10-54			481.9	465.4
10-55			498.4	481.2
10-56			413.4	397.1
10-57			498.4	481.2
10-58			408.5	409.2
10-59			425.5	409.2
10-60			444.5	428.4
10-61			422.5	323.4
10-62			487.5	471.3
10-63			473.5	474.2
10-64			498.4	498.1
10-65			447.5	448.2
10-66			459.5	460.2
10-67			443.5	434.2
10-68			443.5	444.2
10-69			451.6	452.3
10-70			409.5	410.2
10-71			409.5	410.2
10-72			427.5	428.2

EXAMPLE 11

SYNTHESIS OF REPRESENTATIVE COMPOUNDS



Step A <u>1-(2,6-difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-5-(1-ethoxyvinyl)-6-methyluracil</u>

A solution of 1-(2,6-difluorobenzyl-3-[(2R)-tert-butylcarbonylamino-2-phenyl]ethyl-5-bromo-6-methyluracil **1** (500 mg, 0.91 mmol), tributyl(ethoxyvinyl)tin (0.39 mL) and $(Ph_3P)_4Pd(0)$ (105 mg) in dioxane (5 mL) was heated at 100°C under nitrogen for 2 hours. The reaction mixture was concentrated *in vacuo* and the crude product **2** was used for next step. MS: 442 (MH+-Boc).

Step B <u>1-(2,6-Difluorobenzyl-3-[(2R)-tertbutyloxycarbonylamino-2-phenyl]ethyl-5-acetyl-6-methyluracil</u>

A solution of 1-(2,6-difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-5-(1-ethoxyvinyl)-6-methyluracil **2** (490 mg) in THF (10 mL) was treated with 2.5M aqueous HCl (3 mL) and stirred at r.t. for one hour. The reaction mixture was neutralized with $NaHCO_3$ and concentrated in vacuo to remove THF. The product was extracted with ethyl acetate. The extract was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a brown solid. Chromatography on silica gel with 1:2 to 1:1 ethyl acetate/hexanes gave compound **3** as a white solid (227

mg, 50% yield); 1H NMR:1.37 (s, 9H), 2.38 (s, 3H), 2.58 (s, 3H), 4.12 (dd, J = 4.2, 10.0Hz, 1H), 4.65 (dd, J = 6.5, 10.0Hz, 1H), 5.20 (m, 1H), 5.40 (d, J = 12.0Hz, 1H), 5.49 (d, J = 12.0Hz, 1H), 5.58 (d, J = 6.0Hz, 1H), 6.92 (t, J = 8.0Hz, 2H), 7.38 (m, 6H); MS: 414 (MH+- Boc).

Step C 1-(2,6-Difluorobenzyl-3-[(2R)-tertbutoxycarbonylamino-2-phenyl]ethyl-5-(3-dimethylamino-1-oxopropenyl)-6-methyluracil

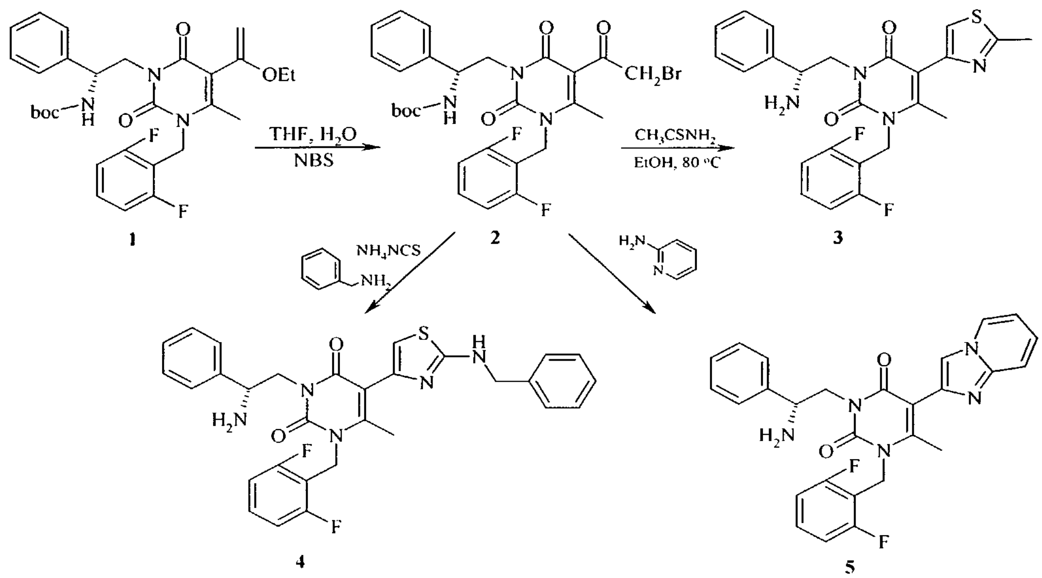
1-(2,6-Difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-5-acetyl-6-methyluracil **3** (44 mg) was suspended in DMFDMA (1.0 mL) and heated at 50°C for 1 hour. The product was purified on silica gel with 1:1 ethyl acetate/hexanes to give compound **4** as a yellow oil; 1H NMR: 1.39 (s, 9H), 2.36 (s, 3H), 2.84 (s, 6H), 4.05 (m, 1H), 4.30 (m, 1H), 4.66 (d, J = 12.0Hz, 1H), 5.03 (m, 1H), 5.20 (d, J = 12Hz, 1H), 5.46 (d, J = 12Hz, 1H), 5.84 (d, J = 7Hz, 1H), 6.64 (d, J = 12.0Hz, 1H), 6.87 (t, J = 8.0Hz, 2H), 7.20-7.40 (m, 6H); MS: 596 (MH+).

Step D 1-(2,6-Difluorobenzyl-3-[(2R)-amino-2-phenyl]ethyl-5-(isoxazol-5-yl)-6-methyluracil

A mixture of 1-(2,6-difluorobenzyl-3-[(2R)-tertbutoxycarbonylamino-2-phenyl]ethyl-5-(3-dimethylamino-1-oxopropenyl)-6-methyluracil **4** (95 mg), hydroxylamine hydrochloride (150 mg), sodium carbonate (18 mg) in methanol (5 mL) was acidified with acetic acid to pH~4. The mixture was then heated at 120°C for 1.5 hours, cooled down to r.t., filtered, and concentrated *in vacuo* to give the protected product. MS: 539 (MH+). The protected product was dissolved in dichloromethane (2 mL), treated with TFA (1 mL), and stirred at r.t. for 1 hour. Concentration *in vacuo* followed by purification on silica gel eluting with 1% aq. NH_4OH in ethyl acetate gave product **5**; MS: 439 (MH+); 1H NMR (CD_3OD): 3.05 (s, 3H), 4.70 (m, 1H), 4.55 (m, 2H), 5.48 (d, J = 12.0Hz, 1H), 5.60 (d, J = 12.0Hz, 1H), 7.00 (t, J = 8.0Hz, 2H), 7.30-7.65 (m, 7H), 8.50 (d, J = 6.0Hz, 1H).

EXAMPLE 12

SYNTHESIS OF REPRESENTATIVE COMPOUNDS



Step A <u>1-(2,6-Difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-5-bromoacetyl-6-methyluracil</u>

A solution of 1-(2,6-difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-5-(1-ethoxyvinyl)-6-methyluracil **1** (3.68g, 6.8 mmol) in THF (120 mL) and water (120 mL) was treated with N-bromosuccinimide (2.3 g) at r.t. and the mixture was stirred for 4 hours. THF was removed *in vacuo* and the product which precipitated on standing was collected by filtration and was washed with ether to give white solid **2** (1.6g, 40%);1H NMR: 1.39 (s, 9H), 2.40 (s, 3H), 4.04 (dd, J = 2.0, 7.0Hz, 1H), 4.36 (d, J = 7.0Hz, 1H), 4.10 (d, J = 5.5Hz, 1H), 4.56 (d, J = 5.5Hz, 1H), 55.50 (m, 1H), 5.24 (d, J = 12.0Hz, 1H), 5.40 (brs, 1H), 5.50 (d, J = 12.0Hz, 1H), 6.94 (t, J = 8.0Hz, 1H), 7.36 (m, 6H); MS: 492 (MH+).

Step B <u>1-(2,6-Difluorobenzyl-3-[(2R)-amino-2-phenyl]ethyl-5-(5-methylthiazol-4-yl)-6-methyluracil</u>

A solution of 1-(2,6-difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-5-bromoacetyl-6-methyluracil (100 mg, 0.17 mmol) and thioacetamide (30

mg, 0.4 mmol) in ethanol (2 mL) was heated at 80°C in a sealed reaction vessel for 3 hours. The reaction mixture was then concentrated *in vacuo* to give an oil and LCMS indicated protected product; MS: 569 (MH+). The protected product was dissolved in dichloromethane (2 mL) and treated with TFA (1 mL) at r.t. for 1 hour, and concentrated in vacuo. The product was purified on silica gel eluting with 5% aq. NH_4OH in ethyl acetate to give yellow solid **3**; 1H NMR: 2.12 (s, 3H), 2.71 (s, 3H), 4.15-4.70 (m, 3H), 5.66 (s, 2H), 7.00 (t, J = 8.0Hz, 2H), 7.30 (m, 7H); MS: 469 (MH+).

Step C 1-(2,6-Difluorobenzyl-3-[(2R)-amino-2-phenyl]ethyl-5-(5-benzylaminolthiazol-4-yl)-6-methyluracil

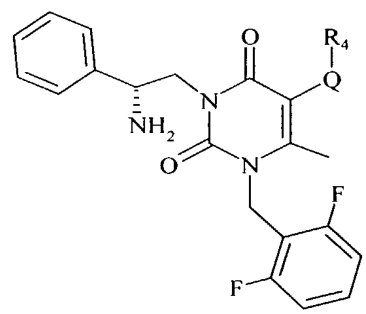
A solution of 1-(2,6-difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-5-bromoacetyl-6-methyluracil **2** (35 mg) and ammonium thioisocyanate (10 mg) in ethanol (1 mL) was heated at 80°C in a sealed reaction vessel for 1 hour. Benzylamine (0.2 mL) was added and the mixture was heated at 80°C overnight. The reaction mixture was then concentrated *in vacuo*, and the protected product was dissolved in dichloromethane (1 mL) and treated with TFA (1 mL) at r.t. for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified on silica gel with 5% aq. NH_4OH in ethyl acetate to give product **4** as a yellow solid; ^1H NMR: 2.25 (s, 3H), 4.05 (dd, J = 3.0, 7.5Hz, 1H), 4.28 (dd, J = 6.5, 7.5Hz, 1H), 4.42 (m, 1H), 4.44 (s, 2H), 5.32 (d, J = 12.0Hz, 1H), 5.36 (d, J = 12.0Hz, 1H), 6.54 (s, 1H), 6.92 (t, J = 8.0Hz, 2H), 7.20-7.50 (m, 11H); MS: 560 (MH^+).

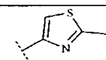
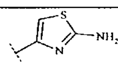
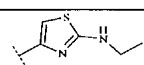
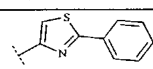
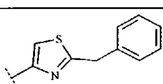
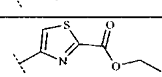
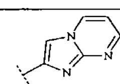
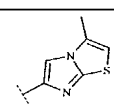
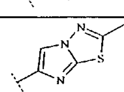
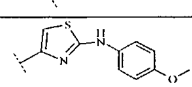
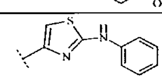
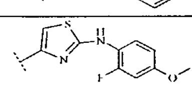
Step D 1-(2,6-Difluorobenzyl-3-[(2R)-amino-2-phenyl]ethyl-5-(imidazolo[1,2-a]pyrid-2-yl)-6-methyluracil

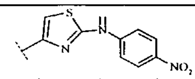
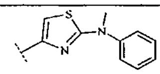
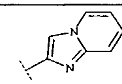
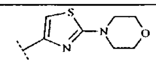
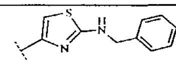
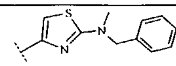
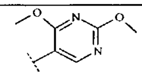
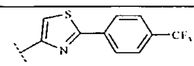
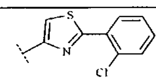
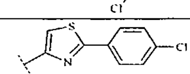
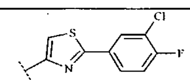
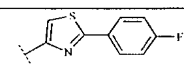
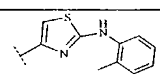
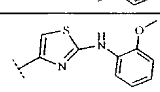
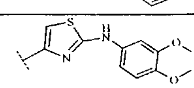
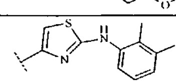
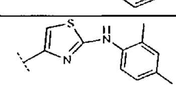
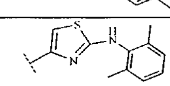
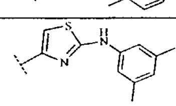
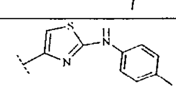
A mixture of 1-(2,6-difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-5-bromoacetyl-6-methyluracil **2** (35 mg) and 2-aminopyridine (7 mg) in ethanol was heated at 80°C overnight. The reaction mixture was then concentrated *in vacuo*, and the protected product was dissolved in dichloromethane (1 mL) and treated with TFA (1 mL) at r.t. for 1 hour. After concentration *in vacuo*, the product **5** was purified on preparative HPLC; 1H NMR: 2.32 (s, 3H), 4.04 (m, 1H), 4.67 (m, 2H), 5.17

(d, J = 16.2Hz, 1H), 5.41 (d, J = 16.2Hz, 1H), 6.92 (t, J = 8.1Hz, 2H), 7.24-7.40 (m, 7H), 7.73 (m, 1H), 7.80 (m, 1H), 8.03 (s, 1H), 8.30 (brs, 3H), 8.44 (d, J = 5.5Hz, 1H); MS: 488 (MH+).

Table 12

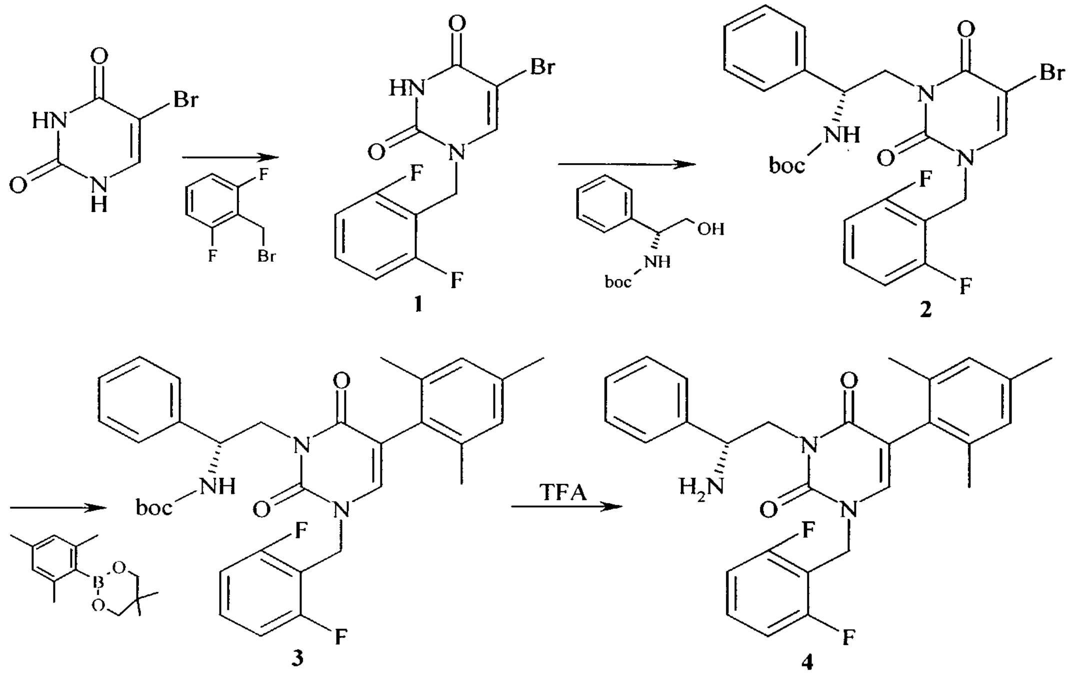


Cpd. No.	$-Q-R_4$	MW (calc.)	(obs.)
12-1		468.5	469.1
12-2		469.5	470.1
12-3		497.6	498.2
12-4		530.6	531.1
12-5		544.6	545.2
12-6		526.6	527.2
12-7		488.5	489.2
12-8		507.6	508.2
12-9		508.6	509.1
12-10		575.6	576.2
12-11		545.6	546.2
12-12		563.6	564.2

12-13		590.6	591.1
12-14		559.6	560.2
12-15		487.5	488.2
12-16		539.6	540.2
12-17		559.6	560.2
12-18		573.7	574.2
12-19		509.5	510
12-20		598.6	599.2
12-21		565.0	565.2
12-22		565.0	565.1
12-23		583.0	583.1
12-24		548.6	549.2
12-25		559.6	560.2
12-26		575.6	576.2
12-27		605.7	606.3
12-28		573.7	574.2
12-29		573.7	574.2
12-30		573.7	574.2
12-31		573.7	574.2
12-32		559.6	560.2

EXAMPLE 13

SYNTHESIS OF REPRESENTATIVE COMPOUNDS



Step A. <u>5-Bromo-1-(2,6-difluorobenzyl)uracil</u>

A suspension of 5-bromouracil (18.45 g, 96.6 mmol) in 300 mL of dichloroethane was treated with N,O-bis(trimethylsilyl)acetamide (48 mL, 39.5 g, 194 mmol). The reaction mixture was heated at 80°C for 3 hr under the nitrogen. The solution was cooled down to ambient temperature, 2,6-difluorobenzyl bromide (25 g, 120 mmol) was added and the reaction mixture was heated at 80°C overnight under the protection of nitrogen. The reaction was cooled down, quenched with MeOH (15 mL), and partitioned between dichloromethane (500 mL) and water (250 mL). The organic layer was washed with brine, dried (sodium sulfate), and evaporated to give a solid. The crude product was triturated with ether, filtered, and washed with ether three times to give compound **1** (15.2 g, 50%) as a white solid; MS (CI) *m/z* 316.90, 318.90 (MH^+).

Step B 1-(2,6-Difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-5-bromouracil

A solution of (*R*)-*N*-(*tert*-butoxycarbonyl)-2-phenylglycinol (14.97 g, 63.1 mmol) in anhydrous THF (300 mL) was treated with 5-bromo-1-(2,6-difluorobenzyl)uracil **1** (20 g, 63.1 mmol) and triphenylphosphine (20.68 g, 78.8 mmol) at ambient temperature, then diisopropylazodicarboxylate (15.52 mL, 15.94 g, 78.8 mmol) in THF (30 mL) was introduced via a dropping funnel. The reaction mixture was stirred at ambient temperature for 16 h and volatiles were evaporated. The residue was purified by flash chromatography (silica, 25% EtOAc/hexanes) to give compound **2** (31.15 g, 92.1 %) as a white solid, MS (CI) *m/z* 436.0, 438.0 (MH^+–Boc).

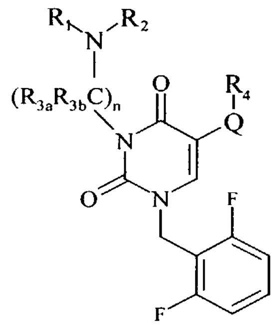
Step C 1-(2,6-Difluorobenzyl-3-[(2R)-tert-butoxycarbonylamino-2-phenyl]ethyl-5-(2,4,6-trimethylphenyl)uracil

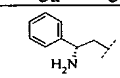
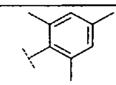
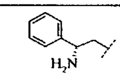
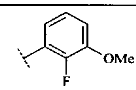
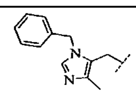
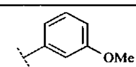
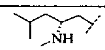
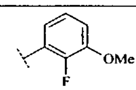
To compound **2** (134 mg, 0.25 mmol) in toluene/H_2O/EtOH (6/3.75/0.75 mL) was added 2,4,6-trimethylphenyl boronic acid ester (87 mg, 1.5 eq), K_2CO_3 (86 mg, 2.5 eq), and saturated $Ba(OH)_2$/water (0.1 mL). The reaction mixture was deoxygenated with N_2 for 10 min, tetrakis(triphenylphosphine) palladium (0) (29 mg, 0.1 eq) was added and the reaction mixture was heated at 100°C overnight under the protection of N_2. The reaction mixture was partitioned between brine and EtOAc. The organic layer was dried (sodium sulfate), evaporated, purified by flash chromatography (silica, 25% EtOAc/hexanes) to give compound **3** (130 mg) as a pale yellow oil.

Step D 1-(2,6-Difluorobenzyl-3-[(2R)-amino-2-phenyl]ethyl-5-(2,4,6-trimethylphenyl)uracil

TFA (3 mL) was added to a solution of **3** (130 mg, 0.22 mmol) in dichloromethane (3 mL) and the reaction mixture was stirred at ambient temperature for 2 hours. Volatiles were evaporated and the residue was partitioned between saturated $NaHCO_3$/water and EtOAc. The organic layer was dried (sodium sulfate), evaporated, and purified by prep TLC eluting with 5% MeOH in CH_2Cl_2 to give compound **4**, MS (CI) *m/z* 476.2 (MH^+).

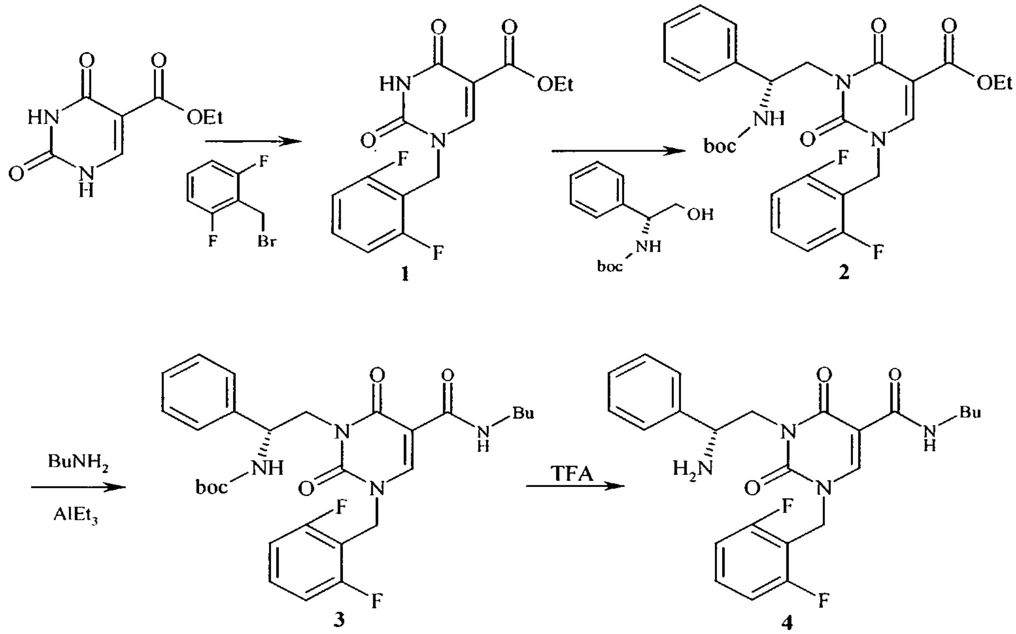
Table 13



Cpd. No.	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	(obs.)
13-1			475.5	476.2
13-2			481.5	482
13-3			528.6	529
13-4			475.5	476.2

EXAMPLE 14

SYNTHESIS OF REPRESENTATIVE COMPOUNDS



Step A 1-(2,6-Difluorobenzyl)-5-carbethoxyuracil

5-Carbethoxyuracil (5 g, 27.15 mmol) and N,O-bis(trimethylsilyl)acetamide (13.4 mL, 2 eq) in dichloroethane(35 mL) were heated at 80°C for 2 hours. Difluorobenzyl bromide (8.4 g, 1.5 eq) was added and the reaction mixture was heated at 80°C for 16 hours. The reaction was quenched with methanol and partitioned between methylene chloride and sodium bicarbonate solution. The organic layer was washed with brine, dried and concentrated *in vacuo* and the residue was triturated with ether to give compound **1** as a white solid (3.26 g).

Step B 1-(2,6-Difluorobenzyl-3-[(2R)-tert-butoxycarbonylamino-2-phenyl]ethyl-5-carbethoxyuracil

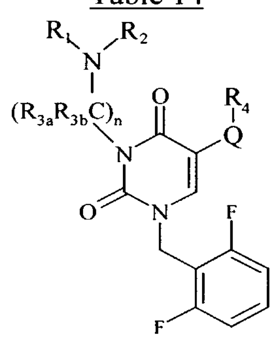
A solution of (*R*)-*N*-(*tert*-butoxycarbonyl)-2-phenylglycinol (316 mg, 1.33 mmol) in anhydrous THF (30 mL) was treated with 1-(2,6-difluorobenzyl)-5-carbethoxyuracil **1** (413 mg, 1.33 mmol) and triphenylphosphine (525 mg, 2 mmol) at ambient temperature, then diisopropylazodicarboxylate (460 mg, 2 mmol) in THF (5

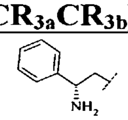
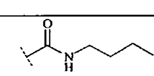
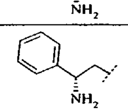
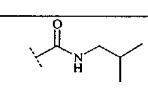
mL) was introduced via a dropping funnel. The reaction mixture was stirred at ambient temperature for 5 h and volatiles were evaporated. The residue was purified by flash chromatography (silica, 35% EtOAc/hexanes) to give compound **2** (427 mg) as a white foam.

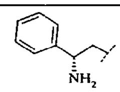
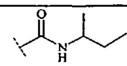
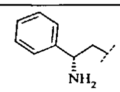
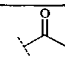
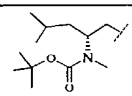
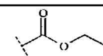
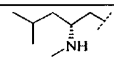
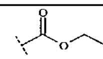
Step C <u>1-(2,6-Difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-5-n-butylamidouracil</u>

A solution of triethylaluminum (1.9 M in toluene, 0.26 mL, 0.5 mmol) was added to n-butylamine (0.1 mL, 1 mmol) in dichloroethane and the reaction mixture was sealed under nitrogen and stirred for ½ hour. 1-(2,6-Difluorobenzyl-3-[(2R)-tertbutylcarbonylamino-2-phenyl]ethyl-5-carbethoxyuracil **2** was added and the mixture was stirred at 70-80°C for 12 hours to give **3**. Trifluoroacetic acid (1 mL) was added and the reaction mixture was stirred for 1 hour. The mixture was concentrated *in vacuo* and the residue was partitioned between methylene chloride and sodium carbonate solution. The organic layer was washed with brine, dried and concentrated to give a residue which was purified by prep HPLC to give compound **4** (56 mg, MH^+ 457).

<u>Table 14</u>

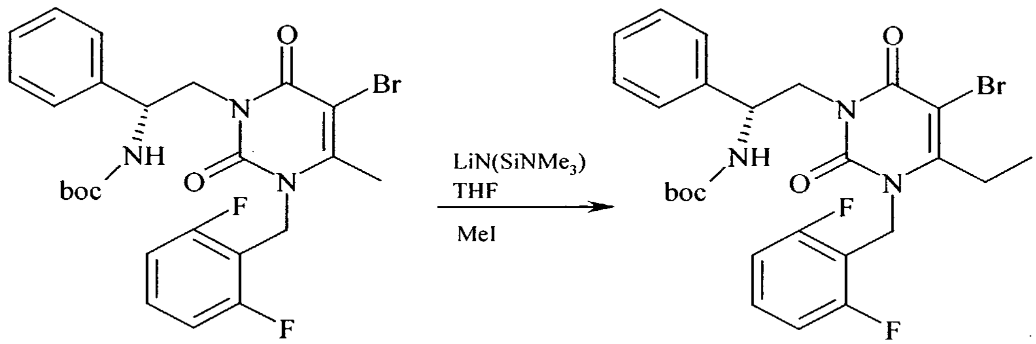


Cpd. No.	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	MW (obs.)
14-1			456.5	457.2
14-2			456.5	457.2

14-3			456.5	457.2
14-4			413.4	414.1
14-5			523.6	424.2
14-6			423.5	424.2

EXAMPLE 15

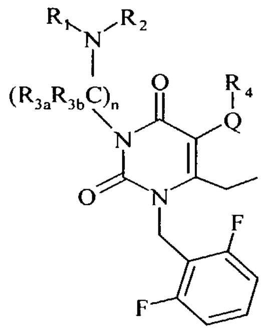
SYNTHESIS OF REPRESENTATIVE COMPOUNDS

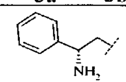
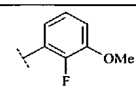
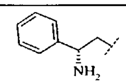
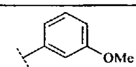
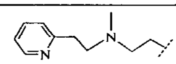
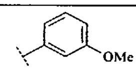
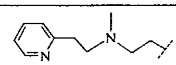
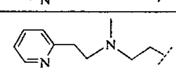
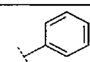
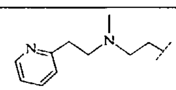
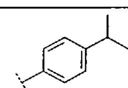
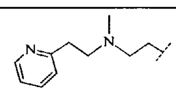
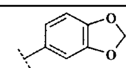
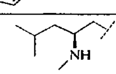
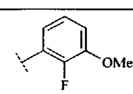
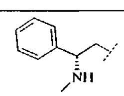
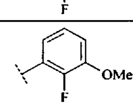


Step A <u>1-(2,6-Difluorobenzyl-3-[(2R)-tert-butoxycarbonylamino-2-phenyl]ethyl-5-bromo-6-ethyluracil</u>

1-(2,6-Difluorobenzyl-3-[(2R)-tert-butoxycarbonylamino-2-phenyl]ethyl-5-bromo-6-methyluracil **1** (550 mg, 1 mmol) was dissolved in THF (10 mL) and the solution was cooled to 0°C. Lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.3 mL, 1.3 mmol) was added dropwise and the reaction was stirred for 40 minutes at 0°C. Iodomethane (0.093 mL, 1.5 mmol) was added dropwise and after 30 minutes, water was added and the mixture extracted with ethyl acetate. Concentration *in vacuo* gave compound **2** as a yellow foam.

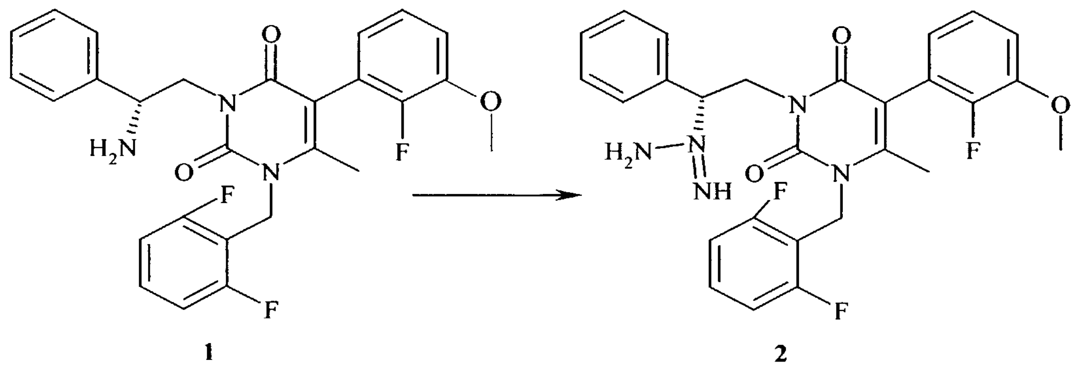
Table 15



Cpd. No.	NR_1R_2-$(CR_{3a}CR_{3b})_n$-	-Q-R_4	MW (calc.)	MW (obs.)
15-1			509.5	510.2
15-2			491.5	492
15-3			534.6	535
15-4		H	428.5	429
15-5			504.6	505
15-6			546.65	
15-7			548.58	549.2
15-8			503.6	504.3
15-9			523.6	524

EXAMPLE 16

SYNTHESIS OF REPRESENTATIVE COMPOUNDS



Step A 1-(2,6-Difluorobenzyl)-3-(4-methyl-2R-guanidopentyl)-5-(2-fluoro-3-methoxyphenyl)-6-methyluracil

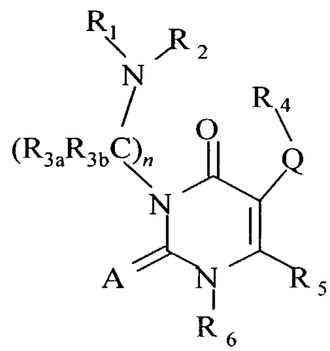
A solution of 1-(2,6-difluorobenzyl)-3-(4-methyl-2R-aminopentyl)-5-(2-fluoro-3-methoxyphenyl)-6-methyluracil **1** (75 mg), (1H)-pyrazole-1-carboxamidine hydrochloride (23 mg) diisopropylethylamine (21 mg) in anhydrous DMF was heated at 40-50 °C overnight (0.5 mL). The reaction mixture was treated with water and the product was extracted with ethyl acetate. The extract was dried over $MgSO_4$, filtered and concentrated *in vacuo* and the residue was purified on silica gel ($Et_3N/MeOH/CHCl_3$ (2:5:93) as elutant) to give white solid **2**. MS: 518 (MH^+).

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

We claim:

1. A compound having the following structure:



or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof,

wherein:

Q is a direct bond or $-(CR_{8a}R_{8b})_r-Z-(CR_{10a}R_{10b})_s-$;

A is O, S, or NR_7;

r and s are the same or different and independently 0, 1, 2, 3, 4, 5 or 6;

n is 2, 3 or 4;

Z is a direct bond or -O-, -S-, $-NR_9-$, -SO-, $-SO_2-$, $-OSO_2-$, $-SO_2O-$, $-SO_2NR_9-$, $-NR_9SO_2-$, -CO-, -COO-, -OCO-, $-CONR_9-$, $-NR_9CO-$, $-NR_9CONR_{9a}$, $-OCONR_9-$ or $-NR_9COO-$;

R_1 and R_2 are the same or different and independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, $-C(R_{1a})(=NR_{1b})$, or $-C(NR_{1a}R_{1c})(=NR_{1b})$;

or R_1 and R_2 taken together with the nitrogen atom to which they are attached form a heterocyclic ring or a substituted heterocyclic ring;

R_{3a} and R_{3b} are the same or different and, at each occurrence, independently hydrogen, alkyl, substituted alkyl, alkoxy, alkylthio, alkylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, $-COOR_{14}$ or $-CONR_{14}R_{15}$;

or R_{3a} and R_{3b} taken together with the carbon atom to which they are attached form a homocyclic ring, substituted homocyclic ring, heterocyclic ring or substituted heterocyclic ring;

or R_{3a} and R_{3b} taken together form $=NR_{3c}$;

or R_{3a} and the carbon to which it is attached taken together with R_1 and the nitrogen to which it is attached form a heterocyclic ring or substituted heterocyclic ring;

R_4 is higher alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, $-COR_{11}$, $-COOR_{11}$, $-CONR_{12}R_{13}$, $-OR_{11}$, $-OCOR_{11}$, $-OSO_2R_{11}$, $-SR_{11}$, $-SO_2R_{11}$, $-NR_{12}R_{13}$, $-NR_{11}COR_{12}$, $-NR_{11}CONR_{12}R_{13}$, $-NR_{11}SO_2R_{12}$ or $-NR_{11}SO_2NR_{12}R_{13}$;

R_5 is hydrogen, halogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, alkoxy, alkylthio, alkylamino, cyano or nitro;

R_6 is higher alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

R_7 is hydrogen, $-SO_2R_{11}$, cyano, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; and

R_{1a}, R_{1b}, R_{1c}, R_{3c}, R_{8a}, R_{8b}, R_9, R_{9a}, R_{10a}, R_{10b}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are the same or different and, at each occurrence, independently hydrogen, acyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl;

or R_{1a} and R_{1b}, R_{8a} and R_{8b}, R_{10a} and R_{10b}, R_{12} and R_{13}, or R_{14} and R_{15} taken together with the atom or atoms to which they are attached form a homocyclic ring, substituted homocyclic ring, heterocyclic ring or substituted heterocyclic ring.

2. The compound of claim 1 wherein A is O.

3. The compound of claim 1 wherein A is S.

4. The compound of claim 1 wherein A is NR_7.

5. The compound of claim 1 wherein R_1 is aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl.

6. The compound of claim 5 wherein heterocycle is heteroaryl, substituted heterocycle is substituted heteroaryl, heterocyclealkyl is heteroarylalkyl, and substituted heterocyclealkyl is substituted heteroarylalkyl.

7. The compound of claim 7 wherein R_1 is heteroarylalkyl or substituted heteroarylalkyl.

8. The compound of claim 1 wherein R_1 is phenylalkyl or substituted phenylalkyl.

9. The compound of claim 1 wherein R_1 is benzyl.

10. The compound of claim 1 wherein R_1 is hydrogen or lower alkyl.

11. The compound of claim 1 wherein R_2 is hydrogen, alkyl or substituted alkyl.

12. The compound of claim 1 wherein R_2 is hydrogen or methyl.

13. The compound of claim 1 wherein Q is a direct bond.

14. The compound of claim 1 wherein Q is $-(CR_{8a}R_{8b})_r$-Z-$(CR_{10a}R_{10b})_s$-.

15. The compound of claim 1 wherein R_{3a} and R_{3b} are, at each occurrence, hydrogen.

16. The compound of claim 1 wherein R_{3a} is hydrogen, alkyl, aryl or arylalkyl.

17. The compound of claim 1 wherein R_{3a} is hydrogen, methyl, isobutyl, cyclohexyl, phenyl or benzyl.

18. The compound of claim 1 wherein R_{3b} is, at each occurrence, hydrogen.

19. The compound of claim 1 wherein n is 1.

20. The comound of claim 1 wherein n is 2.

21. The compound of claim 20 wherein $-(R_{3a}R_{3b}C)_n-$ has the structure $-C(R_{3a})(R_{3b})CH_2-$.

22. The compound of claim 21 wherein R_{3a} is benzyl.

23. The compound of claim 21 wherein R_{3a} is alkyl.

24. The comound of claim 23 wherein R_{3a} is isobutyl or cyclohexyl.

25. The compound of claim 21 wherein R_{3b} is hydrogen or methyl.

26. The compound of claim 1 wherein R_4 is substituted aryl or substituted heterocycle.

27. The compound of claim 1 wherein R_4 is substituted phenyl.

28. The compound of claim 27 wherein R_4 is phenyl substituted with halogen, alkoxy, or both halogen and alkoxy.

29. The compound of claim 1 wherein R_5 is H, lower alkyl or substituted lower alkyl.

30. The compound of claim 1 wherein R_5 is hydrogen or methyl.

31. The compound of claim 1 wherein R_6 is aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl.

32. The compound of claim 1 wherein R_6 is arylalkyl, substituted arylalkyl, heteroarylalkyl or substituted heteroarylalkyl.

33. The compounds of claim 1 wherein R_6 is benzyl or substituted benzyl.

34. The compound of claim 1 wherein R_6 is benzyl substituted with two halogens.

35. The compound of claim 1 wherein Q is a bond and R_4 is substituted aryl or heterocycle.

36. The compound of claim 1 wherein R_1 is $-CH_2$(heteroaryl) or $-CH_2CH_2$(heteroaryl).

37. The compound of claim 1 wherein R_1 and R_2 taken together with the nitrogen atom to which they are attached form a heterocyclic ring or substituted heterocyclic ring.

38. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

39. A method for antagonizing gonadotropin-releasing hormone in a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1 or a pharmaceutical composition of claim 38.

40. A method for treating an sex-hormone related condition of a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1 or a pharmaceutical composition of claim 38.

41. The method of claim 40 wherein the sex-hormone related condition is cancer, benign prostatic hypertrophy or myoma of the uterus.

42. The method of claim 41 wherein the cancer is prostatic cancer, uterine cancer, breast cancer or pituitary gonadotroph adenomas.

43. The method of claim 41 wherein the sex-hormone related condition is endometriosis, polycystic ovarian disease, uterine fibroids or precocious puberty.

44. A method for preventing pregnancy of a subject in need thereof, comprising administering an effective amount of a compound of claim 1 or a pharmaceutical composition of claim 38.

45. A method for treating lupus erythematosis, irritable bowel syndrome, premenstrual syndrome, hirsutism, short stature or sleep disorders of a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1 or a pharmaceutical composition of claim 38.